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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly lung cancer, are disclosed. Illustrative compositions comprise one or more lung tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly lung cancer.



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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of
5 cancer, such as lung cancer. The invention is more specifically related to polypeptides,
comprising at least a portion of a lung tumor protein, and to polynucleotides encoding
such polypeptides. Such polypeptides and polynucleotides are useful in pharmaceutical
compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of
lung cancer.

10 BACKGROUND OF THE INVENTION

Field of the Invention

Cancer is a significant health problem throughout the world. Although
advances have been made in detection and therapy of cancer, no vaccine or other
universally successful method for prevention and/or treatment is currently available.

15 Current therapies, which are generally based on a combination of chemotherapy or
surgery and radiation, continue to prove inadequate in many patients.

Description of Related Art

Lung cancer is the primary cause of cancer death among both men and
women in the U.S., with an estimated 172,000 new cases being reported in 1994. The
20 five-year survival rate among all lung cancer patients, regardless of the stage of disease
at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among
cases detected while the disease is still localized. However, only 16% of lung cancers
are discovered before the disease has spread.

In spite of considerable research into therapies for these and other
25 cancers, lung cancer remains difficult to diagnose and treat effectively. Accordingly,
there is a need in the art for improved methods for detecting and treating such cancers.
The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

- (a) sequences provided in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 5 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;
- 10 (b) complements of the sequences provided in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 15 420, 424, 428, 431, 434, 442, 447, 450 and 467;
- (c) sequences consisting of at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 75 and 100 contiguous residues of a sequence provided in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 20 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;
- (d) sequences that hybridize to a sequence provided in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 25 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467, under moderate or highly stringent conditions;
- 30 (e) sequences having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identity to a sequence of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30,

32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 5 434, 442, 447, 450 and 467; and

(f) degenerate variants of a sequence provided in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 10 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of lung tumors samples tested, at a level that 15 is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

20 The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO:152, 155, 156, 165, 166, 169, 170, 172, 174, 176, 226-252, 338-344, 346, 350, 357, 361, 363, 365, 367, 369, 376-382, 387-419, 423, 427, 430, 433, 441, 443, 446, 449, 451-466 and 468-469.

25 In certain preferred embodiments, the polypeptides and/or polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or 30 derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity

of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO:152, 155, 156, 165, 166, 169, 170, 172, 174, 176, 226-252, 338-344, 346, 350, 357, 361, 363, 365, 367, 369, 376-382, 387-419, 423, 427, 430, 433, 441, 443, 446, 449 and
5 451-466, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364,
10 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical
15 compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, the pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or
20 polynucleotide of the invention and an immunostimulant, such as an adjuvant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

25 Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins
5 that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, e.g., vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise
10 one or more polypeptide segments for facilitating the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The
15 patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a
20 patient a pharmaceutical composition as recited above. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological
25 sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological
30 sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a lung cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the

sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the
5 patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b)
10 detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one
15 oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

20 In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b)
25 using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as
30 monoclonal antibodies, that bind to a polypeptide as described above, as well as

diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are
5 hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

- SEQ ID NO:1 is the determined cDNA sequence for LST-S1-2
SEQ ID NO:2 is the determined cDNA sequence for LST-S1-28
10 SEQ ID NO:3 is the determined cDNA sequence for LST-S1-90
SEQ ID NO:4 is the determined cDNA sequence for LST-S1-144
SEQ ID NO:5 is the determined cDNA sequence for LST-S1-133
SEQ ID NO:6 is the determined cDNA sequence for LST-S1-169
SEQ ID NO:7 is the determined cDNA sequence for LST-S2-6
15 SEQ ID NO:8 is the determined cDNA sequence for LST-S2-11
SEQ ID NO:9 is the determined cDNA sequence for LST-S2-17
SEQ ID NO:10 is the determined cDNA sequence for LST-S2-25
SEQ ID NO:11 is the determined cDNA sequence for LST-S2-39
SEQ ID NO:12 is a first determined cDNA sequence for LST-S2-43
20 SEQ ID NO:13 is a second determined cDNA sequence for LST-S2-43
SEQ ID NO:14 is the determined cDNA sequence for LST-S2-65
SEQ ID NO:15 is the determined cDNA sequence for LST-S2-68
SEQ ID NO:16 is the determined cDNA sequence for LST-S2-72
SEQ ID NO:17 is the determined cDNA sequence for LST-S2-74
25 SEQ ID NO:18 is the determined cDNA sequence for LST-S2-103
SEQ ID NO:19 is the determined cDNA sequence for LST-S2-N1-1F
SEQ ID NO:20 is the determined cDNA sequence for LST-S2-N1-2A
SEQ ID NO:21 is the determined cDNA sequence for LST-S2-N1-4H
SEQ ID NO:22 is the determined cDNA sequence for LST-S2-N1-5A
30 SEQ ID NO:23 is the determined cDNA sequence for LST-S2-N1-6B

- SEQ ID NO:24 is the determined cDNA sequence for LST-S2-N1-7B
SEQ ID NO:25 is the determined cDNA sequence for LST-S2-N1-7H
SEQ ID NO:26 is the determined cDNA sequence for LST-S2-N1-8A
SEQ ID NO:27 is the determined cDNA sequence for LST-S2-N1-8D
5 SEQ ID NO:28 is the determined cDNA sequence for LST-S2-N1-9A
SEQ ID NO:29 is the determined cDNA sequence for LST-S2-N1-9E
SEQ ID NO:30 is the determined cDNA sequence for LST-S2-N1-10A
SEQ ID NO:31 is the determined cDNA sequence for LST-S2-N1-10G
SEQ ID NO:32 is the determined cDNA sequence for LST-S2-N1-11A
10 SEQ ID NO:33 is the determined cDNA sequence for LST-S2-N1-12C
SEQ ID NO:34 is the determined cDNA sequence for LST-S2-N1-12E
SEQ ID NO:35 is the determined cDNA sequence for LST-S2-B1-3D
SEQ ID NO:36 is the determined cDNA sequence for LST-S2-B1-6C
SEQ ID NO:37 is the determined cDNA sequence for LST-S2-B1-5D
15 SEQ ID NO:38 is the determined cDNA sequence for LST-S2-B1-5F
SEQ ID NO:39 is the determined cDNA sequence for LST-S2-B1-6G
SEQ ID NO:40 is the determined cDNA sequence for LST-S2-B1-8A
SEQ ID NO:41 is the determined cDNA sequence for LST-S2-B1-8D
SEQ ID NO:42 is the determined cDNA sequence for LST-S2-B1-10A
20 SEQ ID NO:43 is the determined cDNA sequence for LST-S2-B1-9B
SEQ ID NO:44 is the determined cDNA sequence for LST-S2-B1-9F
SEQ ID NO:45 is the determined cDNA sequence for LST-S2-B1-12D
SEQ ID NO:46 is the determined cDNA sequence for LST-S2-I2-2B
SEQ ID NO:47 is the determined cDNA sequence for LST-S2-I2-5F
25 SEQ ID NO:48 is the determined cDNA sequence for LST-S2-I2-6B
SEQ ID NO:49 is the determined cDNA sequence for LST-S2-I2-7F
SEQ ID NO:50 is the determined cDNA sequence for LST-S2-I2-8G
SEQ ID NO:51 is the determined cDNA sequence for LST-S2-I2-9E
SEQ ID NO:52 is the determined cDNA sequence for LST-S2-I2-12B
30 SEQ ID NO:53 is the determined cDNA sequence for LST-S2-H2-2C
SEQ ID NO:54 is the determined cDNA sequence for LST-S2-H2-1G

- SEQ ID NO:55 is the determined cDNA sequence for LST-S2-H2-4G
SEQ ID NO:56 is the determined cDNA sequence for LST-S2-H2-3H
SEQ ID NO:57 is the determined cDNA sequence for LST-S2-H2-5G
SEQ ID NO:58 is the determined cDNA sequence for LST-S2-H2-9B
5 SEQ ID NO:59 is the determined cDNA sequence for LST-S2-H2-10H
SEQ ID NO:60 is the determined cDNA sequence for LST-S2-H2-12D
SEQ ID NO: 61 is the determined cDNA sequence for LST-S3-2
SEQ ID NO: 62 is the determined cDNA sequence for LST-S3-4
SEQ ID NO: 63 is the determined cDNA sequence for LST-S3-7
10 SEQ ID NO: 64 is the determined cDNA sequence for LST-S3-8
SEQ ID NO: 65 is the determined cDNA sequence for LST-S3-12
SEQ ID NO: 66 is the determined cDNA sequence for LST-S3-13
SEQ ID NO: 67 is the determined cDNA sequence for LST-S3-14
SEQ ID NO: 68 is the determined cDNA sequence for LST-S3-16
15 SEQ ID NO: 69 is the determined cDNA sequence for LST-S3-21
SEQ ID NO: 70 is the determined cDNA sequence for LST-S3-22
SEQ ID NO: 71 is the determined cDNA sequence for LST-S1-7
SEQ ID NO: 72 is the determined cDNA sequence for LST-S1-A-1E
SEQ ID NO: 73 is the determined cDNA sequence for LST-S1-A-1G
20 SEQ ID NO: 74 is the determined cDNA sequence for LST-S1-A-3E
SEQ ID NO: 75 is the determined cDNA sequence for LST-S1-A-4E
SEQ ID NO: 76 is the determined cDNA sequence for LST-S1-A-6D
SEQ ID NO: 77 is the determined cDNA sequence for LST-S1-A-8D
SEQ ID NO: 78 is the determined cDNA sequence for LST-S1-A-10A
25 SEQ ID NO: 79 is the determined cDNA sequence for LST-S1-A-10C
SEQ ID NO: 80 is the determined cDNA sequence for LST-S1-A-9D
SEQ ID NO: 81 is the determined cDNA sequence for LST-S1-A-10D
SEQ ID NO: 82 is the determined cDNA sequence for LST-S1-A-9H
SEQ ID NO: 83 is the determined cDNA sequence for LST-S1-A-11D
30 SEQ ID NO: 84 is the determined cDNA sequence for LST-S1-A-12D
SEQ ID NO: 85 is the determined cDNA sequence for LST-S1-A-11E

- SEQ ID NO: 86 is the determined cDNA sequence for LST-S1-A-12E
- SEQ ID NO: 87 is the determined cDNA sequence for L513S (T3).
- SEQ ID NO: 88 is the determined cDNA sequence for L513S contig 1.
- SEQ ID NO: 89 is a first determined cDNA sequence for L514S.
- 5 SEQ ID NO: 90 is a second determined cDNA sequence for L514S.
- SEQ ID NO: 91 is a first determined cDNA sequence for L516S.
- SEQ ID NO: 92 is a second determined cDNA sequence for L516S.
- SEQ ID NO: 93 is the determined cDNA sequence for L517S.
- SEQ ID NO: 94 is the extended cDNA sequence for LST-S1-169 (also known as
- 10 L519S).
- SEQ ID NO: 95 is a first determined cDNA sequence for L520S.
- SEQ ID NO: 96 is a second determined cDNA sequence for L520S.
- SEQ ID NO: 97 is a first determined cDNA sequence for L521S.
- SEQ ID NO: 98 is a second determined cDNA sequence for L521S.
- 15 SEQ ID NO: 99 is the determined cDNA sequence for L522S.
- SEQ ID NO: 100 is the determined cDNA sequence for L523S.
- SEQ ID NO: 101 is the determined cDNA sequence for L524S.
- SEQ ID NO: 102 is the determined cDNA sequence for L525S.
- SEQ ID NO: 103 is the determined cDNA sequence for L526S.
- 20 SEQ ID NO: 104 is the determined cDNA sequence for L527S.
- SEQ ID NO: 105 is the determined cDNA sequence for L528S.
- SEQ ID NO: 106 is the determined cDNA sequence for L529S.
- SEQ ID NO: 107 is a first determined cDNA sequence for L530S.
- SEQ ID NO: 108 is a second determined cDNA sequence for L530S.
- 25 SEQ ID NO: 109 is the determined full-length cDNA sequence for L531S short form
- SEQ ID NO: 110 is the amino acid sequence encoded by SEQ ID NO: 109.
- SEQ ID NO: 111 is the determined full-length cDNA sequence for L531S long form
- SEQ ID NO: 112 is the amino acid sequence encoded by SEQ ID NO: 111.
- SEQ ID NO: 113 is the determined full-length cDNA sequence for L520S.
- 30 SEQ ID NO: 114 is the amino acid sequence encoded by SEQ ID NO: 113.
- SEQ ID NO: 115 is the determined cDNA sequence for contig 1.

- SEQ ID NO: 116 is the determined cDNA sequence for contig 3.
SEQ ID NO: 117 is the determined cDNA sequence for contig 4.
SEQ ID NO: 118 is the determined cDNA sequence for contig 5.
SEQ ID NO: 119 is the determined cDNA sequence for contig 7.
- 5 SEQ ID NO: 120 is the determined cDNA sequence for contig 8.
SEQ ID NO: 121 is the determined cDNA sequence for contig 9.
SEQ ID NO: 122 is the determined cDNA sequence for contig 10.
SEQ ID NO: 123 is the determined cDNA sequence for contig 12.
SEQ ID NO: 124 is the determined cDNA sequence for contig 11.
- 10 SEQ ID NO: 125 is the determined cDNA sequence for contig 13 (also known as L761P).
SEQ ID NO: 126 is the determined cDNA sequence for contig 15.
SEQ ID NO: 127 is the determined cDNA sequence for contig 16.
SEQ ID NO: 128 is the determined cDNA sequence for contig 17.
- 15 SEQ ID NO: 129 is the determined cDNA sequence for contig 19.
SEQ ID NO: 130 is the determined cDNA sequence for contig 20.
SEQ ID NO: 131 is the determined cDNA sequence for contig 22.
SEQ ID NO: 132 is the determined cDNA sequence for contig 24.
SEQ ID NO: 133 is the determined cDNA sequence for contig 29.
- 20 SEQ ID NO: 134 is the determined cDNA sequence for contig 31.
SEQ ID NO: 135 is the determined cDNA sequence for contig 33.
SEQ ID NO: 136 is the determined cDNA sequence for contig 38.
SEQ ID NO: 137 is the determined cDNA sequence for contig 39.
SEQ ID NO: 138 is the determined cDNA sequence for contig 41.
- 25 SEQ ID NO: 139 is the determined cDNA sequence for contig 43.
SEQ ID NO: 140 is the determined cDNA sequence for contig 44.
SEQ ID NO: 141 is the determined cDNA sequence for contig 45.
SEQ ID NO: 142 is the determined cDNA sequence for contig 47.
SEQ ID NO: 143 is the determined cDNA sequence for contig 48.
- 30 SEQ ID NO: 144 is the determined cDNA sequence for contig 49.
SEQ ID NO: 145 is the determined cDNA sequence for contig 50.

- SEQ ID NO: 146 is the determined cDNA sequence for contig 53.
SEQ ID NO: 147 is the determined cDNA sequence for contig 54.
SEQ ID NO: 148 is the determined cDNA sequence for contig 56.
SEQ ID NO: 149 is the determined cDNA sequence for contig 57.
5 SEQ ID NO: 150 is the determined cDNA sequence for contig 58.
SEQ ID NO: 151 is the full-length cDNA sequence for L530S.
SEQ ID NO: 152 is the amino acid sequence encoded by SEQ ID NO: 151
SEQ ID NO: 153 is the full-length cDNA sequence of a first variant of L514S
SEQ ID NO: 154 is the full-length cDNA sequence of a second variant of L514S
10 SEQ ID NO: 155 is the amino acid sequence encoded by SEQ ID NO: 153.
SEQ ID NO: 156 is the amino acid sequence encoded by SEQ ID NO: 154.
SEQ ID NO: 157 is the determined cDNA sequence for contig 59.
SEQ ID NO: 158 is the full-length cDNA sequence for L763P (also referred to as contig 22).
15 SEQ ID NO: 159 is the amino acid sequence encoded by SEQ ID NO: 158.
SEQ ID NO: 160 is the full-length cDNA sequence for L762P (also referred to as contig 17).
SEQ ID NO: 161 is the amino acid sequence encoded by SEQ ID NO: 160.
SEQ ID NO: 162 is the determined cDNA sequence for L515S.
20 SEQ ID NO: 163 is the full-length cDNA sequence of a first variant of L524S.
SEQ ID NO: 164 is the full-length cDNA sequence of a second variant of L524S.
SEQ ID NO: 165 is the amino acid sequence encoded by SEQ ID NO: 163.
SEQ ID NO: 166 is the amino acid sequence encoded by SEQ ID NO: 164.
SEQ ID NO: 167 is the full-length cDNA sequence of a first variant of L762P.
25 SEQ ID NO: 168 is the full-length cDNA sequence of a second variant of L762P.
SEQ ID NO: 169 is the amino acid sequence encoded by SEQ ID NO: 167.
SEQ ID NO: 170 is the amino acid sequence encoded by SEQ ID NO: 168.
SEQ ID NO: 171 is the full-length cDNA sequence for L773P (also referred to as contig 56).
30 SEQ ID NO: 172 is the amino acid sequence encoded by SEQ ID NO: 171.
SEQ ID NO: 173 is an extended cDNA sequence for L519S.

- SEQ ID NO: 174 is the amino acid sequence encoded by SEQ ID NO: 174.
SEQ ID NO: 175 is the full-length cDNA sequence for L523S.
SEQ ID NO: 176 is the amino acid sequence encoded by SEQ ID NO: 175.
SEQ ID NO: 177 is the determined cDNA sequence for LST-sub5-7A.
- 5 SEQ ID NO: 178 is the determined cDNA sequence for LST-sub5-8G.
SEQ ID NO: 179 is the determined cDNA sequence for LST-sub5-8H.
SEQ ID NO: 180 is the determined cDNA sequence for LST-sub5-10B.
SEQ ID NO: 181 is the determined cDNA sequence for LST-sub5-10H.
SEQ ID NO: 182 is the determined cDNA sequence for LST-sub5-12B.
- 10 SEQ ID NO: 183 is the determined cDNA sequence for LST-sub5-11C.
SEQ ID NO: 184 is the determined cDNA sequence for LST-sub6-1c.
SEQ ID NO: 185 is the determined cDNA sequence for LST-sub6-2f.
SEQ ID NO: 186 is the determined cDNA sequence for LST-sub6-2G.
SEQ ID NO: 187 is the determined cDNA sequence for LST-sub6-4d.
- 15 SEQ ID NO: 188 is the determined cDNA sequence for LST-sub6-4e.
SEQ ID NO: 189 is the determined cDNA sequence for LST-sub6-4f.
SEQ ID NO: 190 is the determined cDNA sequence for LST-sub6-3h.
SEQ ID NO: 191 is the determined cDNA sequence for LST-sub6-5d.
SEQ ID NO: 192 is the determined cDNA sequence for LST-sub6-5h.
- 20 SEQ ID NO: 193 is the determined cDNA sequence for LST-sub6-6h.
SEQ ID NO: 194 is the determined cDNA sequence for LST-sub6-7a.
SEQ ID NO: 195 is the determined cDNA sequence for LST-sub6-8a.
SEQ ID NO: 196 is the determined cDNA sequence for LST-sub6-7d.
SEQ ID NO: 197 is the determined cDNA sequence for LST-sub6-7e.
- 25 SEQ ID NO: 198 is the determined cDNA sequence for LST-sub6-8e.
SEQ ID NO: 199 is the determined cDNA sequence for LST-sub6-7g.
SEQ ID NO: 200 is the determined cDNA sequence for LST-sub6-9f.
SEQ ID NO: 201 is the determined cDNA sequence for LST-sub6-9h.
SEQ ID NO: 202 is the determined cDNA sequence for LST-sub6-11b.
- 30 SEQ ID NO: 203 is the determined cDNA sequence for LST-sub6-11c.
SEQ ID NO: 204 is the determined cDNA sequence for LST-sub6-12c.

- SEQ ID NO: 205 is the determined cDNA sequence for LST-sub6-12e.
SEQ ID NO: 206 is the determined cDNA sequence for LST-sub6-12f.
SEQ ID NO: 207 is the determined cDNA sequence for LST-sub6-11g.
SEQ ID NO: 208 is the determined cDNA sequence for LST-sub6-12g.
5 SEQ ID NO: 209 is the determined cDNA sequence for LST-sub6-12h.
SEQ ID NO: 210 is the determined cDNA sequence for LST-sub6-II-1a.
SEQ ID NO: 211 is the determined cDNA sequence for LST-sub6-II-2b.
SEQ ID NO: 212 is the determined cDNA sequence for LST-sub6-II-2g.
SEQ ID NO: 213 is the determined cDNA sequence for LST-sub6-II-1h.
10 SEQ ID NO: 214 is the determined cDNA sequence for LST-sub6-II-4a.
SEQ ID NO: 215 is the determined cDNA sequence for LST-sub6-II-4b.
SEQ ID NO: 216 is the determined cDNA sequence for LST-sub6-II-3e.
SEQ ID NO: 217 is the determined cDNA sequence for LST-sub6-II-4f.
SEQ ID NO: 218 is the determined cDNA sequence for LST-sub6-II-4g.
15 SEQ ID NO: 219 is the determined cDNA sequence for LST-sub6-II-4h.
SEQ ID NO: 220 is the determined cDNA sequence for LST-sub6-II-5c.
SEQ ID NO: 221 is the determined cDNA sequence for LST-sub6-II-5e.
SEQ ID NO: 222 is the determined cDNA sequence for LST-sub6-II-6f.
SEQ ID NO: 223 is the determined cDNA sequence for LST-sub6-II-5g.
20 SEQ ID NO: 224 is the determined cDNA sequence for LST-sub6-II-6g.
SEQ ID NO: 225 is the amino acid sequence for L528S.
SEQ ID NO: 226-251 are synthetic peptides derived from L762P.
SEQ ID NO: 252 is the expressed amino acid sequence of L514S.
SEQ ID NO: 253 is the DNA sequence corresponding to SEQ ID NO: 252.
25 SEQ ID NO: 254 is the DNA sequence of a L762P expression construct.
SEQ ID NO: 255 is the determined cDNA sequence for clone 23785.
SEQ ID NO: 256 is the determined cDNA sequence for clone 23786.
SEQ ID NO: 257 is the determined cDNA sequence for clone 23788.
SEQ ID NO: 258 is the determined cDNA sequence for clone 23790.
30 SEQ ID NO: 259 is the determined cDNA sequence for clone 23793.
SEQ ID NO: 260 is the determined cDNA sequence for clone 23794.

- SEQ ID NO: 261 is the determined cDNA sequence for clone 23795.
SEQ ID NO: 262 is the determined cDNA sequence for clone 23796.
SEQ ID NO: 263 is the determined cDNA sequence for clone 23797.
SEQ ID NO: 264 is the determined cDNA sequence for clone 23798.
5 SEQ ID NO: 265 is the determined cDNA sequence for clone 23799.
SEQ ID NO: 266 is the determined cDNA sequence for clone 23800.
SEQ ID NO: 267 is the determined cDNA sequence for clone 23802.
SEQ ID NO: 268 is the determined cDNA sequence for clone 23803.
SEQ ID NO: 269 is the determined cDNA sequence for clone 23804.
10 SEQ ID NO: 270 is the determined cDNA sequence for clone 23805.
SEQ ID NO: 271 is the determined cDNA sequence for clone 23806.
SEQ ID NO: 272 is the determined cDNA sequence for clone 23807.
SEQ ID NO: 273 is the determined cDNA sequence for clone 23808.
SEQ ID NO: 274 is the determined cDNA sequence for clone 23809.
15 SEQ ID NO: 275 is the determined cDNA sequence for clone 23810.
SEQ ID NO: 276 is the determined cDNA sequence for clone 23811.
SEQ ID NO: 277 is the determined cDNA sequence for clone 23812.
SEQ ID NO: 278 is the determined cDNA sequence for clone 23813.
SEQ ID NO: 279 is the determined cDNA sequence for clone 23815.
20 SEQ ID NO: 280 is the determined cDNA sequence for clone 25298.
SEQ ID NO: 281 is the determined cDNA sequence for clone 25299.
SEQ ID NO: 282 is the determined cDNA sequence for clone 25300.
SEQ ID NO: 283 is the determined cDNA sequence for clone 25301
SEQ ID NO: 284 is the determined cDNA sequence for clone 25304
25 SEQ ID NO: 285 is the determined cDNA sequence for clone 25309.
SEQ ID NO: 286 is the determined cDNA sequence for clone 25312.
SEQ ID NO: 287 is the determined cDNA sequence for clone 25317.
SEQ ID NO: 288 is the determined cDNA sequence for clone 25321.
SEQ ID NO: 289 is the determined cDNA sequence for clone 25323.
30 SEQ ID NO: 290 is the determined cDNA sequence for clone 25327.
SEQ ID NO: 291 is the determined cDNA sequence for clone 25328.

- SEQ ID NO:292 is the determined cDNA sequence for clone 25332.
SEQ ID NO:293 is the determined cDNA sequence for clone 25333.
SEQ ID NO:294 is the determined cDNA sequence for clone 25336.
SEQ ID NO:295 is the determined cDNA sequence for clone 25340.
5 SEQ ID NO:296 is the determined cDNA sequence for clone 25342.
SEQ ID NO:297 is the determined cDNA sequence for clone 25356.
SEQ ID NO:298 is the determined cDNA sequence for clone 25357.
SEQ ID NO:299 is the determined cDNA sequence for clone 25361.
SEQ ID NO:300 is the determined cDNA sequence for clone 25363.
10 SEQ ID NO:301 is the determined cDNA sequence for clone 25397.
SEQ ID NO:302 is the determined cDNA sequence for clone 25402.
SEQ ID NO:303 is the determined cDNA sequence for clone 25403.
SEQ ID NO:304 is the determined cDNA sequence for clone 25405.
SEQ ID NO:305 is the determined cDNA sequence for clone 25407.
15 SEQ ID NO:306 is the determined cDNA sequence for clone 25409.
SEQ ID NO:307 is the determined cDNA sequence for clone 25396.
SEQ ID NO:308 is the determined cDNA sequence for clone 25414.
SEQ ID NO:309 is the determined cDNA sequence for clone 25410.
SEQ ID NO:310 is the determined cDNA sequence for clone 25406.
20 SEQ ID NO:311 is the determined cDNA sequence for clone 25306.
SEQ ID NO:312 is the determined cDNA sequence for clone 25362.
SEQ ID NO:313 is the determined cDNA sequence for clone 25360.
SEQ ID NO:314 is the determined cDNA sequence for clone 25398.
SEQ ID NO:315 is the determined cDNA sequence for clone 25355.
25 SEQ ID NO:316 is the determined cDNA sequence for clone 25351.
SEQ ID NO:317 is the determined cDNA sequence for clone 25331.
SEQ ID NO:318 is the determined cDNA sequence for clone 25338.
SEQ ID NO:319 is the determined cDNA sequence for clone 25335.
SEQ ID NO:320 is the determined cDNA sequence for clone 25329.
30 SEQ ID NO:321 is the determined cDNA sequence for clone 25324.
SEQ ID NO:322 is the determined cDNA sequence for clone 25322.

- SEQ ID NO:323 is the determined cDNA sequence for clone 25319.
- SEQ ID NO:324 is the determined cDNA sequence for clone 25316.
- SEQ ID NO:325 is the determined cDNA sequence for clone 25311.
- SEQ ID NO:326 is the determined cDNA sequence for clone 25310.
- 5 SEQ ID NO:327 is the determined cDNA sequence for clone 25302.
- SEQ ID NO:328 is the determined cDNA sequence for clone 25315.
- SEQ ID NO:329 is the determined cDNA sequence for clone 25308.
- SEQ ID NO:330 is the determined cDNA sequence for clone 25303.
- SEQ ID NO:331-337 are the cDNA sequences of isoforms of the p53 tumor suppressor
- 10 homologue, p63 (also referred to as L530S).
- SEQ ID NO:338-344 are the amino acid sequences encoded by SEQ ID NO:331-337, respectively
- SEQ ID NO:345 is a second cDNA sequence for the antigen L763P.
- SEQ ID NO:346 is the amino acid sequence encoded by the sequence of SEQ ID NO:
- 15 345.
- SEQ ID NO:347 is a determined full-length cDNA sequence for L523S.
- SEQ ID NO:348 is the amino acid sequence encoded by SEQ ID NO: 347.
- SEQ ID NO:349 is the cDNA sequence encoding the N-terminal portion of L773P.
- SEQ ID NO:350 is the amino acid sequence of the N-terminal portion of L773P.
- 20 SEQ ID NO:351 is the DNA sequence for a fusion of Ra12 and the N-terminal portion of L763P.
- SEQ ID NO:352 is the amino acid sequence of the fusion of Ra12 and the N-terminal portion of L763P.
- SEQ ID NO:353 is the DNA sequence for a fusion of Ra12 and the C-terminal portion
- 25 of L763P.
- SEQ ID NO:354 is the amino acid sequence of the fusion of Ra12 and the C-terminal portion of L763P.
- SEQ ID NO:355 is a primer.
- SEQ ID NO:356 is a primer.
- 30 SEQ ID NO:357 is the protein sequence of expressed recombinant L762P.
- SEQ ID NO:358 is the DNA sequence of expressed recombinant L762P.

- SEQ ID NO:359 is a primer.
- SEQ ID NO:360 is a primer.
- SEQ ID NO:361 is the protein sequence of expressed recombinant L773P A.
- SEQ ID NO:362 is the DNA sequence of expressed recombinant L773P A.
- 5 SEQ ID NO:363 is an epitope derived from clone L773P polypeptide.
- SEQ ID NO:364 is a polynucleotide encoding the polypeptide of SEQ ID NO:363.
- SEQ ID NO:365 is an epitope derived from clone L773P polypeptide.
- SEQ ID NO:366 is a polynucleotide encoding the polypeptide of SEQ ID NO:365.
- SEQ ID NO:367 is an epitope consisting of amino acids 571-590 of SEQ ID NO:161,
- 10 clone L762P.
- SEQ ID NO:368 is the full-length DNA sequence for contig 13 (SEQ ID NO:125), also referred to as L761P.
- SEQ ID NO:369 is the protein sequence encoded by the DNA sequence of SEQ ID NO:368.
- 15 SEQ ID NO:370 is an L762P DNA sequence from nucleotides 2071-2130.
- SEQ ID NO:371 is an L762P DNA sequence from nucleotides 1441-1500.
- SEQ ID NO:372 is an L762P DNA sequence from nucleotides 1936-1955.
- SEQ ID NO:373 is an L762P DNA sequence from nucleotides 2620-2679.
- SEQ ID NO:374 is an L762P DNA sequence from nucleotides 1801-1860.
- 20 SEQ ID NO:375 is an L762P DNA sequence from nucleotides 1531-1591.
- SEQ ID NO:376 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO:373.
- SEQ ID NO:377 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO:370.
- 25 SEQ ID NO:378 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO:372.
- SEQ ID NO:379 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO:374.
- SEQ ID NO:380 is the amino acid sequence of the L762P peptide encoded by SEQ ID
- 30 NO:371.

- SEQ ID NO:381 is the amino acid sequence of the L762P peptide encoded by SEQ ID NO:375.
- SEQ ID NO:382 is the amino acid sequence of an epitope of L762P.
- SEQ ID NO:383-386 are PCR primers.
- 5 SEQ ID NO:387-395 are the amino acid sequences of L773P peptides.
- SEQ ID NO:396-419 are the amino acid sequences of L523S peptides.
- SEQ ID NO:420 is the determined cDNA sequence for clone #19014.
- SEQ ID NO:421 is the forward primer PDM-278 for the L514S-13160 coding region.
- SEQ ID NO:422 is the reverse primer PDM-278 for the L514S-13160 coding region.
- 10 SEQ ID NO:423 is the amino acid sequence for the expressed recombinant L514S.
- SEQ ID NO:424 is the DNA coding sequence for the recombinant L514S.
- SEQ ID NO:425 is the forward primer PDM-414 for the L523S coding region.
- SEQ ID NO:426 is the reverse primer PDM-414 for the L523S coding region.
- SEQ ID NO:427 is the amino acid sequence for the expressed recombinant L523S.
- 15 SEQ ID NO:428 is the DNA coding sequence for the recombinant L523S.
- SEQ ID NO:429 is the reverse primer PDM-279 for the L762PA coding region.
- SEQ ID NO:430 is the amino acid sequence for the expressed recombinant L762PA.
- SEQ ID NO:431 is the DNA coding sequence for the recombinant L762PA.
- SEQ ID NO:432 is the reverse primer PDM-300 for the L773P coding region.
- 20 SEQ ID NO:433 is the amino acid sequence of the expressed recombinant L773P.
- SEQ ID NO:434 is the DNA coding sequence for the recombinant L773P.
- SEQ ID NO:435 is the forward primer for TCR Valpha8.
- SEQ ID NO:436 is the reverse primer for TCR Valpha8.
- SEQ ID NO:437 is the forward primer for TCR Vbeta8.
- 25 SEQ ID NO:438 is the reverse primer for TCR Vbeta8.
- SEQ ID NO:439 is the TCR Valpha DNA sequence of the TCR clone specific for the lung antigen L762P.
- SEQ ID NO:440 is the TCR Vbeta DNA sequence of the TCR clone specific for the lung antigen L762P.
- 30 SEQ ID NO:441 is the amino acid sequence of L763 peptide #2684.

- SEQ ID NO:442 is the predicted full-length cDNA for the cloned partial sequence of clone L529S (SEQ ID NO:106).
- SEQ ID NO:443 is the deduced amino acid sequence encoded by SEQ ID NO:442.
- SEQ ID NO:444 is the forward primer PDM-734 for the coding region of clone L523S.
- 5 SEQ ID NO:445 is the reverse primer PDM-735 for the coding region of clone L523S.
- SEQ ID NO:446 is the amino acid sequence for the expressed recombinant L523S.
- SEQ ID NO:447 is the DNA coding sequence for the recombinant L523S.
- SEQ ID NO:448 is another forward primer PDM-733 for the coding region of clone L523S.
- 10 SEQ ID NO:449 is the amino acid sequence for a second expressed recombinant L523S.
- SEQ ID NO:450 is the DNA coding sequence for a second recombinant L523S.
- SEQ ID NO:451 corresponds to amino acids 86-110, an epitope of L514S-specific in the generation of antibodies.
- SEQ ID NO:452 corresponds to amino acids 21-45, an epitope of L514S-specific in the
- 15 generation of antibodies.
- SEQ ID NO:453 corresponds to amino acids 121-135, an epitope of L514S-specific in the generation of antibodies.
- SEQ ID NO:454 corresponds to amino acids 440-460, an epitope of L523S-specific in the generation of antibodies.
- 20 SEQ ID NO:455 corresponds to amino acids 156-175, an epitope of L523S-specific in the generation of antibodies.
- SEQ ID NO:456 corresponds to amino acids 326-345, an epitope of L523S-specific in the generation of antibodies.
- SEQ ID NO:457 corresponds to amino acids 40-59, an epitope of L523S-specific in the
- 25 generation of antibodies.
- SEQ ID NO:458 corresponds to amino acids 80-99, an epitope of L523S-specific in the generation of antibodies.
- SEQ ID NO:459 corresponds to amino acids 160-179, an epitope of L523S-specific in the generation of antibodies.
- 30 SEQ ID NO:460 corresponds to amino acids 180-199, an epitope of L523S-specific in the generation of antibodies.

SEQ ID NO:461 corresponds to amino acids 320-339, an epitope of L523S-specific in the generation of antibodies.

SEQ ID NO:462 corresponds to amino acids 340-359, an epitope of L523S-specific in the generation of antibodies.

- 5 SEQ ID NO:463 corresponds to amino acids 370-389, an epitope of L523S-specific in the generation of antibodies.

SEQ ID NO:464 corresponds to amino acids 380-399, an epitope of L523S-specific in the generation of antibodies.

- 10 SEQ ID NO:465 corresponds to amino acids 37-55, an epitope of L523S-recognized by the L523S-specific CTL line 6B1.

SEQ ID NO:466 corresponds to amino acids 41-51, the mapped antigenic epitope of L523S-recognized by the L523S-specific CTL line 6B1.

SEQ ID NO:467 corresponds to the DNA sequence which encodes SEQ ID NO:466.

SEQ ID NO:468 corresponds to the amino acids of peptide 16, 17 of hL523S.

- 15 SEQ ID NO:469 corresponds to the amino acids of peptide 16, 17 of mL523S

DETAILED DESCRIPTION OF THE INVENTION

- The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly lung cancer. As described further below, illustrative compositions of the present invention include, but are not restricted
- 20 to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.*, T cells).

- The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology,
- 25 microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); Maniatis et al. *Molecular Cloning: A Laboratory Manual* (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid
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Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

5 All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

10 As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-
15 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic
20 determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-
25 82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a
30 polynucleotide sequence set forth in any one of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29,

30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 5 431, 434, 442, 447, 450 and 467. Certain illustrative polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NO:152, 155, 156, 165, 166, 169, 170, 172, 174, 176, 226-252, 338-344, 346, 350, 357, 361, 363, 365, 367, 369, 376-382, 387-419, 423, 427, 430, 433, 441, 443, 446, 449, 451-466 and 468-469.

10 The polypeptides of the present invention are sometimes herein referred to as lung tumor proteins or lung tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in lung tumor samples. Thus, a "lung tumor polypeptide" or "lung tumor protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide 15 sequence encoding such a polypeptide, that is expressed in a substantial proportion of lung tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of lung tumor samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal tissues, as determined using a 20 representative assay provided herein. A lung tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

 In certain preferred embodiments, the polypeptides of the invention are 25 immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with lung cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring 30 Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of

antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An
5 "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press,
10 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and
15 antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of
20 the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic
25 activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other illustrative immunogenic portions will contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids),
30 relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic
5 fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in
10 the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more,
15 including all intermediate lengths, of a polypeptide compositions set forth herein, such as those set forth in SEQ ID NO:152, 155, 156, 165, 166, 169, 170, 172, 174, 176, 226-252, 338-344, 346, 350, 357, 361, 363, 365, 367, 369, 376-382 and 387-419, 441, 443, 446, 449, 451-466 and 468-469, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54,
20 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467.

25 In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth
30 herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention,

one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

Table 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are:

isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

5 It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5
10 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

15 As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−
20 2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even
25 more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those
30 of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of
5 nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic
10 nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may
15 represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain non-conservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or
20 alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally
25 directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be
30 "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two

sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402

and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for
5 Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is
10 reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in
15 the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of
20 matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises
25 at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological
30 and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to

desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements

responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

5 The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91, 1997).

10 In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is
15 incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application
20 60/158,585; *see also*, Skeiky et al., *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ra12 fusion
25 polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A.

Other preferred Ra12 polynucleotides generally comprise at least about
15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300
30 nucleotides that encode a portion of a Ra12 polypeptide.

Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology* 10:795-798,

1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4⁺ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially

interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large
5 chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and
10 plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be
15 DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules
20 and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and immunogenic variant or derivative, of such a sequence.

25 Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168,
30 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434,

442, 447, 450 and 467, complements of a polynucleotide sequence set forth in any one of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NO:1-3, 6-8, 10-13, 15-27, 29, 30, 32, 34-49, 51, 52, 54, 55, 57-59, 61-69, 71, 73, 74, 77, 78, 80-82, 84, 86-96, 107-109, 111, 113, 125, 127, 128, 129, 131-133, 142, 144, 148-151, 153, 154, 157, 158, 160, 167, 168, 171, 179, 182, 184-186, 188-191, 193, 194, 198-207, 209, 210, 213, 214, 217, 220-224, 253-337, 345, 347, 349, 358, 362, 364, 365, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the

polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

5 In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more
10 contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the
15 like.

 In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular
20 biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in
25 the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-
30 70°C.

In certain preferred embodiments, the polynucleotides described above, e.g., polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A

- model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) *Unified Approach to Alignment and Phylogenies* pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

- Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

- One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments;

or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this

approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more
5 nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on
10 both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors
15 contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA
20 molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single
25 stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

30 In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a

double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I
5 Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

10 The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence
15 may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kubly, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis
20 procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the
25 template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment
30 into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of

the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region

may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length
5 allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-
10 complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in
15 length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by,
20 for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCRTM technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other
25 recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically
30 desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity,

one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate
5 little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be
10 needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered
15 more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention,
20 polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis
25 is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1,
30 striatal GABA_A receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-

32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m , binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997, 25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*,

Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an

RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stint. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO

94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby.

Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-

500; Hanvey *et al.*, Science. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*,

Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

10 Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made
15 by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome
20 cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring
25 Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example,
30 using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the

manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

5 Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which
10 are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising
15 and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well
20 known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent
25 No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems
30 (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a

nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res.*

16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be
5 retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO
10 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids.*
15 *Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be
20 performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or
25 functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

30 As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing

non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring
5 sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For
10 example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be
20 engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be
30 achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out

transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid
5 lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be
10 advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be
15 used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S.
20 M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such
25 systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may
30 be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. 5 (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques 10 are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus 15 (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat 20 protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression 25 vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, 30 transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-

RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; *Serological Methods, a Laboratory Manual*, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the

encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMLAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant

or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-

binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients
5 with and without a cancer, such as lung cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the
10 absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically
15 significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent.
20 For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In
25 general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep
30 or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a

superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.

- 5 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

- Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.
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- Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.
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A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')₂" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H::V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide

comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody

molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in *Sequences of Proteins of Immunological Interest*, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially

exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an

antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which
5 otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups,
10 sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of
15 different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by
20 serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.
25 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent
30 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides

such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For

example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., *Current Protocols in Immunology*, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

T Cell Receptor Compositions

The T cell receptor (TCR) consists of 2 different, highly variable polypeptide chains, termed the T-cell receptor α and β chains, that are linked by a disulfide bond (Janeway, Travers, Walport. *Immunobiology*. Fourth Ed., 148-159. Elsevier Science Ltd/Garland Publishing. 1999). The α/β heterodimer complexes with the invariant CD3 chains at the cell membrane. This complex recognizes specific antigenic peptides bound to MHC molecules. The enormous diversity of TCR specificities is generated much like immunoglobulin diversity, through somatic gene rearrangement. The β chain genes contain over 50 variable (V), 2 diversity (D), over 10 joining (J) segments, and 2 constant region segments (C). The α chain genes contain over 70 V segments, and over 60 J segments but no D segments, as well as one C segment. During T cell development in the thymus, the D to J gene rearrangement of the β chain occurs, followed by the V gene segment rearrangement to the DJ. This functional VDJ $_{\beta}$ exon is transcribed and spliced to join to a C $_{\beta}$. For the α chain, a V $_{\alpha}$ gene segment rearranges to a J $_{\alpha}$ gene segment to create the functional exon that is then transcribed and spliced to the C $_{\alpha}$. Diversity is further increased during the recombination process by the random addition of P and N-nucleotides between the V, D, and J segments of the β chain and between the V and J segments in the α chain (Janeway, Travers, Walport. *Immunobiology*. Fourth Ed., 98 and 150. Elsevier Science Ltd/Garland Publishing. 1999).

The present invention, in another aspect, provides TCRs specific for a polypeptide disclosed herein, or for a variant or derivative thereof. In accordance with the present invention, polynucleotide and amino acid sequences are provided for the V-J or V-D-J junctional regions or parts thereof for the alpha and beta chains of the T-cell receptor which recognize tumor polypeptides described herein. In general, this aspect of the invention relates to T-cell receptors which recognize or bind tumor polypeptides presented in the context of MHC. In a preferred embodiment the tumor antigens recognized by the T-cell receptors comprise a polypeptide of the present invention. For example, cDNA encoding a TCR specific for a _tumor peptide can be isolated from T cells specific for a tumor polypeptide using standard molecular biological and recombinant DNA techniques.

This invention further includes the T-cell receptors or analogs thereof having substantially the same function or activity as the T-cell receptors of this invention which recognize or bind tumor polypeptides. Such receptors include, but are not limited to, a fragment of the receptor, or a substitution, addition or deletion mutant of a T-cell receptor provided herein. This invention also encompasses polypeptides or peptides that are substantially homologous to the T-cell receptors provided herein or that retain substantially the same activity. The term "analog" includes any protein or polypeptide having an amino acid residue sequence substantially identical to the T-cell receptors provided herein in which one or more residues, preferably no more than 5 residues, more preferably no more than 25 residues have been conservatively substituted with a functionally similar residue and which displays the functional aspects of the T-cell receptor as described herein.

The present invention further provides for suitable mammalian host cells, for example, non-specific T cells, that are transfected with a polynucleotide encoding TCRs specific for a polypeptide described herein, thereby rendering the host cell specific for the polypeptide. The α and β chains of the TCR may be contained on separate expression vectors or alternatively, on a single expression vector that also contains an internal ribosome entry site (IRES) for cap-independent translation of the gene downstream of the IRES. Said host cells expressing TCRs specific for the polypeptide may be used, for example, for adoptive immunotherapy of lung cancer as discussed further below.

In further aspects of the present invention, cloned TCRs specific for a polypeptide recited herein may be used in a kit for the diagnosis of lung cancer. For example, the nucleic acid sequence or portions thereof, of tumor-specific TCRs can be used as probes or primers for the detection of expression of the rearranged genes encoding the specific TCR in a biological sample. Therefore, the present invention further provides for an assay for detecting messenger RNA or DNA encoding the TCR specific for a polypeptide.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of

primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et

al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been
5 developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-
10 539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129; Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived
15 from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is
20 then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK^{sup}(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

25 A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in
30 that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7

promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, *Proc. Natl. Acad. Sci. USA* (1990) 87:6743-6747; Fuerst et al. *Proc. Natl. Acad. Sci. USA* (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science*

252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

5 In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to
10 permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is
15 administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can
20 be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500
25 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful
30 for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described

in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using

standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL[®] adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β -escin, or digitonin.

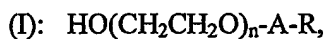
Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol[®] to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL[®] adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in
5 WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL[®] adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-
10 containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF
15 (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn[®]) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the
20 disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



25 wherein, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein n is between 1 and 50, preferably 4-24, most preferably 9; the R component is C_{1-50} , preferably $\text{C}_4\text{-C}_{20}$ alkyl and most preferably C_{12} alkyl, and A is a bond. The
30 concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene

ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck
5 index (12th edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application
10 GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified
15 to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic
20 or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic
25 antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-
30 surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As

an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., *Nature Med.* 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any

methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

10 While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, 15 intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon 20 administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (e.g., 25 a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (see e.g., U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of 30 the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into
5 tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst
10 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as
15 magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance,
20 tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the
25 active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound.
30 Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated

by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as

lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be
5 preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution,
10 the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one
15 dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of
20 course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free
25 amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine,
30 trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be

administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the
15 lungs via nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998 Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit,

Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that
5 are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs,
10 radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that
15 are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and
20 reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur
25 Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

Immunologic approaches to cancer therapy are based on the recognition that cancer cells can often evade the body's defenses against aberrant or foreign cells
30 and molecules, and that these defenses might be therapeutically stimulated to regain the

lost ground, *e.g.* pgs. 623-648 in Klein, Immunology (Wiley-Interscience, New York, 1982). Numerous recent observations that various immune effectors can directly or indirectly inhibit growth of tumors has led to renewed interest in this approach to cancer therapy, *e.g.* Jager, et al., Oncology 2001;60(1):1-7; Renner, et al., Ann Hematol 2000
5 Dec;79(12):651-9.

Four-basic cell types whose function has been associated with antitumor cell immunity and the elimination of tumor cells from the body are: i) B-lymphocytes which secrete immunoglobulins into the blood plasma for identifying and labeling the nonself invader cells; ii) monocytes which secrete the complement proteins that are
10 responsible for lysing and processing the immunoglobulin-coated target invader cells; iii) natural killer lymphocytes having two mechanisms for the destruction of tumor cells, antibody-dependent cellular cytotoxicity and natural killing; and iv) T-lymphocytes possessing antigen-specific receptors and having the capacity to recognize a tumor cell carrying complementary marker molecules (Schreiber, H., 1989, in
15 Fundamental Immunology (ed). W. E. Paul, pp. 923-955).

Cancer immunotherapy generally focuses on inducing humoral immune responses, cellular immune responses, or both. Moreover, it is well established that induction of CD4⁺ T helper cells is necessary in order to secondarily induce either antibodies or cytotoxic CD8⁺ T cells. Polypeptide antigens that are selective or ideally
20 specific for cancer cells, particularly lung cancer cells, offer a powerful approach for inducing immune responses against lung cancer, and are an important aspect of the present invention.

Therefore, in further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for
25 the immunotherapy of lung cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical
30 compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or

conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

5 Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

10 Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T
15 lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody
20 receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Monoclonal antibodies may be labeled with any of a variety of labels for
25 desired selective usages in detection, diagnostic assays or therapeutic applications (as described in U.S. Patent Nos. 6,090,365; 6,015,542; 5,843,398; 5,595,721; and 4,708,930, hereby incorporated by reference in their entirety as if each was incorporated individually). In each case, the binding of the labelled monoclonal antibody to the
30 determinant site of the antigen will signal detection or delivery of a particular therapeutic agent to the antigenic determinant on the non-normal cell. A further object

of this invention is to provide the specific monoclonal antibody suitably labelled for achieving such desired selective usages thereof.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period.

Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided

herein generally permit detection of the level of antigen that binds to the agent in the biological sample.

Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a tumor sequence should be present at a level that is at least two-fold, preferably three-fold, and more preferably five-fold or higher in tumor tissue than in normal tissue of the same type from which the tumor arose. Expression levels of a particular tumor sequence in tissue types different from that in which the tumor arose are irrelevant in certain diagnostic embodiments since the presence of tumor cells can be confirmed by observation of predetermined differential expression levels, e.g., 2-fold, 5-fold, etc, in tumor tissue to expression levels in normal tissue of the same type.

Other differential expression patterns can be utilized advantageously for diagnostic purposes. For example, in one aspect of the invention, overexpression of a tumor sequence in tumor tissue and normal tissue of the same type, but not in other normal tissue types, e.g. PBMCs, can be exploited diagnostically. In this case, the presence of metastatic tumor cells, for example in a sample taken from the circulation or some other tissue site different from that in which the tumor arose, can be identified and/or confirmed by detecting expression of the tumor sequence in the sample, for example using RT-PCR analysis. In many instances, it will be desired to enrich for tumor cells in the sample of interest, e.g., PBMCs, using cell capture or other like techniques.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection

reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about

10 μg , and preferably about 100 ng to about 1 μg , is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with
5 both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at
10 A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody.
15 Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

20 More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to
25 bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.,* incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of
30 that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium

may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support
5 with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide.
10 An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally
15 appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction
20 products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average
25 mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical*
30 *Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot

of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a
5 signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

10 In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution
15 containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent.
20 Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the
25 biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about
30 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use
5 tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within
10 certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For
15 example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is
20 preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on
25 the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is
30 then separated and detected using techniques well known in the art, such as gel electrophoresis.

Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers
5 and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a
10 polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule
15 having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in
20 conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an
25 individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

30 In another aspect of the present invention, cell capture technologies may be used in conjunction, with, for example, real-time PCR to provide a more sensitive

tool for detection of metastatic cells expressing lung tumor antigens. Detection of lung cancer cells in biological samples, e.g., bone marrow samples, peripheral blood, and small needle aspiration samples is desirable for diagnosis and prognosis in lung cancer patients.

5 Immunomagnetic beads coated with specific monoclonal antibodies to surface cell markers, or tetrameric antibody complexes, may be used to first enrich or positively select cancer cells in a sample. Various commercially available kits may be used, including Dynabeads® Epithelial Enrich (DynaL Biotech, Oslo, Norway), StemSep™ (StemCell Technologies, Inc., Vancouver, BC), and RosetteSep (StemCell
10 Technologies). A skilled artisan will recognize that other methodologies and kits may also be used to enrich or positively select desired cell populations. Dynabeads® Epithelial Enrich contains magnetic beads coated with mAbs specific for two glycoprotein membrane antigens expressed on normal and neoplastic epithelial tissues. The coated beads may be added to a sample and the sample then applied to a magnet,
15 thereby capturing the cells bound to the beads. The unwanted cells are washed away and the magnetically isolated cells eluted from the beads and used in further analyses.

RosetteSep can be used to enrich cells directly from a blood sample and consists of a cocktail of tetrameric antibodies that targets a variety of unwanted cells and crosslinks them to glycophorin A on red blood cells (RBC) present in the sample,
20 forming rosettes. When centrifuged over Ficoll, targeted cells pellet along with the free RBC. The combination of antibodies in the depletion cocktail determines which cells will be removed and consequently which cells will be recovered. Antibodies that are available include, but are not limited to: CD2, CD3, CD4, CD5, CD8, CD10, CD11b, CD14, CD15, CD16, CD19, CD20, CD24, CD25, CD29, CD33, CD34, CD36, CD38,
25 CD41, CD45, CD45RA, CD45RO, CD56, CD66B, CD66e, HLA-DR, IgE, and TCR $\alpha\beta$.

Additionally, it is contemplated in the present invention that mAbs specific for lung tumor antigens can be generated and used in a similar manner. For example, mAbs that bind to tumor-specific cell surface antigens may be conjugated to magnetic beads, or formulated in a tetrameric antibody complex, and used to enrich or
30 positively select metastatic lung tumor cells from a sample. Once a sample is enriched or positively selected, cells may be lysed and RNA isolated. RNA may then be

subjected to RT-PCR analysis using lung tumor-specific primers in a real-time PCR assay as described herein. One skilled in the art will recognize that enriched or selected populations of cells may be analyzed by other methods (*e.g. in situ* hybridization or flow cytometry).

5 In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter
10 performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor.
15 One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers
20 may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided
25 herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a
30 monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as

described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

- 5 Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be
10 present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

15 EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF CDNA SEQUENCES ENCODING
LUNG TUMOR POLYPEPTIDES

This example illustrates the isolation of cDNA molecules encoding lung tumor-specific polypeptides from lung tumor cDNA libraries.

20 A. ISOLATION OF CDNA SEQUENCES FROM A LUNG SQUAMOUS CELL
 CARCINOMA LIBRARY

- A human lung squamous cell carcinoma cDNA expression library was constructed from poly A⁺ RNA from a pool of two patient tissues using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies,
25 Gaithersburg, MD) following the manufacturer's protocol. Specifically, lung carcinoma tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using an oligo dT cellulose column as described in

Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with BstXI/EcoRI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following
5 size fractionation with cDNA size fractionation columns (BRL Life Technologies), the cDNA was ligated into the BstXI/NotI site of pcDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human lung cDNA expression library was prepared from a pool of four tissue specimens. The cDNA libraries were
10 characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The lung squamous cell carcinoma library contained 2.7×10^6 independent colonies, with 100% of clones having an insert and the average insert size being 2100 base pairs. The normal lung cDNA library contained 1.4×10^6 independent colonies, with 90% of clones
15 having inserts and the average insert size being 1800 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA

cDNA library subtraction was performed using the above lung squamous cell carcinoma and normal lung cDNA libraries, as described by Hara *et al.* (*Blood*,
20 84:189-199, 1994) with some modifications. Specifically, a lung squamous cell carcinoma-specific subtracted cDNA library was generated as follows. Normal tissue cDNA library (80 µg) was digested with BamHI and XhoI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 133 µl of H₂O, heat-denatured and
25 mixed with 133 µl (133 µg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (67 µl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 µl H₂O to form the driver DNA.

30 To form the tracer DNA, 10 µg lung squamous cell carcinoma cDNA library was digested with NotI and SpeI, phenol chloroform extracted and passed

through Chroma spin-400 columns (Clontech, Palo Alto, CA). Typically, 5 µg of cDNA was recovered after the sizing column. Following ethanol precipitation, the tracer DNA was dissolved in 5 µl H₂O. Tracer DNA was mixed with 15 µl driver DNA and 20 µl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H₂O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into NotI/SpeI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a lung squamous cell carcinoma specific subtracted cDNA library (herein after referred to as "lung subtraction I").

A second lung squamous cell carcinoma specific subtracted cDNA library (referred to as "lung subtraction II") was generated in a similar way to the lung subtraction library I, except that eight frequently recovered genes from lung subtraction I were included in the driver DNA, and 24,000 independent clones were recovered.

To analyze the subtracted cDNA libraries, plasmid DNA was prepared from 320 independent clones, randomly picked from the subtracted lung squamous cell carcinoma specific libraries. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA). The cDNA sequences for sixty isolated clones are provided in SEQ ID NO: 1-60. These sequences were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). No significant homologies were found to the sequences provided in SEQ ID NO: 2, 3, 19, 38 and 46. The sequences of SEQ ID NO: 1, 6-8, 10-13, 15, 17, 18, 20-27, 29, 30, 32, 34-37, 39-45, 47-49, 51, 52, 54, 55 and 57-59 were found to show some homology to previously identified expressed sequence tags (ESTs).

The sequences of SEQ ID NO: 9, 28, 31 and 33 were found to show some homology to previously identified non-human gene sequences and the sequences of SEQ ID NO: 4, 5, 14, 50, 53, 56 and 60 were found to show some homology to gene sequences previously identified in humans.

5 The subtraction procedure described above was repeated using the above lung squamous cell carcinoma cDNA library as the tracer DNA, and the above normal lung tissue cDNA library and a cDNA library from normal liver and heart (constructed from a pool of one sample of each tissue as described above), plus twenty other cDNA clones that were frequently recovered in lung subtractions I and II, as the driver DNA
10 (lung subtraction III). The normal liver and heart cDNA library contained 1.76×10^6 independent colonies, with 100% of clones having inserts and the average insert size being 1600 base pairs. Ten additional clones were isolated (SEQ ID NO: 61-70). Comparison of these cDNA sequences with those in the gene bank as described above, revealed no significant homologies to the sequences provided in SEQ ID NO: 62 and
15 67. The sequences of SEQ ID NO: 61, 63-66, 68 and 69 were found to show some homology to previously isolated ESTs and the sequence provided in SEQ ID NO: 70 was found to show some homology to a previously identified rat gene.

 In further studies, the subtraction procedure described above was repeated using the above lung squamous cell carcinoma cDNA library as the tracer
20 DNA, and a cDNA library from a pool of normal lung, kidney, colon, pancreas, brain, resting PBMC, heart, skin and esophagus as the driver DNA, with esophagus cDNAs making up one third of the driver material. Since esophagus is enriched in normal epithelial cells, including differentiated squamous cells, this procedure is likely to enrich genes that are tumor specific rather than tissues specific. The cDNA sequences
25 of 48 clones determined in this subtraction are provided in SEQ ID NO: 177-224. The sequences of SEQ ID NO: 177, 178, 180, 181, 183, 187, 192, 195-197, 208, 211, 212, 215, 216, 218 and 219 showed some homology to previously identified genes. The sequences of SEQ ID NO: 179, 182, 184-186, 188-191, 193, 194, 198-207, 209 210, 213, 214, 217, 220 and 224 showed some homology to previously determined ESTs.
30 The sequence of SEQ ID NO: 221-223 showed no homology to any previously determined sequence.

B. ISOLATION OF cDNA SEQUENCES FROM A LUNG
ADENOCARCINOMA LIBRARY

A human lung adenocarcinoma cDNA expression library was constructed as described above. The library contained 3.2×10^6 independent colonies, with 100% of clones having an insert and the average insert size being 1500 base pairs. Library subtraction was performed as described above using the normal lung and normal liver and heart cDNA expression libraries described above as the driver DNA. Twenty-six hundred independent clones were recovered.

Initial cDNA sequence analysis from 100 independent clones revealed many ribosomal protein genes. The cDNA sequences for fifteen clones isolated in this subtraction are provided in SEQ ID NO: 71-86. Comparison of these sequences with those in the gene bank as described above revealed no significant homologies to the sequence provided in SEQ ID NO: 84. The sequences of SEQ ID NO: 71, 73, 74, 77, 78 and 80-82 were found to show some homology to previously isolated ESTs, and the sequences of SEQ ID NO: 72, 75, 76, 79, 83 and 85 were found to show some homology to previously identified human genes.

In further studies, a cDNA library (referred to as mets3616A) was constructed from a metastatic lung adenocarcinoma. The determined cDNA sequences of 25 clones sequenced at random from this library are provided in SEQ ID NO: 255-279. The mets3616A cDNA library was subtracted against a cDNA library prepared from a pool of normal lung, liver, pancreas, skin, kidney, brain and resting PBMC. To increase the specificity of the subtraction, the driver was spiked with genes that were determined to be most abundant in the mets3616A cDNA library, such as EF1-alpha, integrin-beta and anticoagulant protein PP4, as well as with cDNAs that were previously found to be differentially expressed in subtracted lung adenocarcinoma cDNA libraries. The determined cDNA sequences of 51 clones isolated from the subtracted library (referred to as mets3616A-S1) are provided in SEQ ID NO: 280-330.

Comparison of the sequences of SEQ ID NO: 255-330 with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 255-258, 260, 262-264, 270, 272, 275, 276, 279, 281, 287, 291, 296, 300 and 310. The sequences of SEQ ID NO: 259, 261, 265-269, 271, 273, 274, 277, 278, 282-285, 288-

290, 292, 294, 297-299, 301, 303-309, 313, 314, 316, 320-324 and 326-330 showed some homology to previously identified gene sequences, while the sequences of SEQ ID NO: 280, 286, 293, 302, 310, 312, 315, 317-319 and 325 showed some homology to previously isolated expressed sequence tags (ESTs).

5

EXAMPLE 2

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for seven representative lung tumor polypeptides described in Example 1 were examined in a variety of normal and tumor tissues using RT-PCR.

10

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 2 µg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 µl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

15

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous cell carcinoma from 3 patients, lung adenocarcinoma, colon tumor from 2 patients, breast tumor and prostate tumor), and thirteen different normal tissues (lung from 4 donors, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, stomach, myocardium, retina and testes). Using a 10-fold amount of cDNA, the antigen LST-S1-90 (SEQ ID NO: 3) was found to be expressed at high levels in lung squamous cell carcinoma and in breast tumor, and at low to undetectable levels in the other tissues examined.

25

The antigen LST-S2-68 (SEQ ID NO: 15) appears to be specific to lung and breast tumor, however, expression was also detected in normal kidney. Antigens LST-S1-169 (SEQ ID NO: 6) and LST-S1-133 (SEQ ID NO: 5) appear to be very abundant in lung tissues (both normal and tumor), with the expression of these two genes being decreased in most of the normal tissues tested. Both LST-S1-169 and LST-S1-133 were also expressed in breast and colon tumors. Antigens LST-S1-6 (SEQ ID NO: 7) and LST-S2-I2-5F (SEQ ID NO: 47) did not show tumor or tissue specific expression, with the expression of LST-S1-28 being rare and only detectable in a few tissues. The antigen LST-S3-7 (SEQ ID NO: 63) showed lung and breast tumor specific expression, with its message only being detected in normal testes when the PCR was performed for 30 cycles. Lower level expression was detected in some normal tissues when the cycle number was increased to 35. Antigen LST-S3-13 (SEQ ID NO: 66) was found to be expressed in 3 out of 4 lung tumors, one breast tumor and both colon tumor samples. Its expression in normal tissues was lower compared to tumors, and was only detected in 1 out of 4 normal lung tissues and in normal tissues from kidney, ovary and retina. Expression of antigens LST-S3-4 (SEQ ID NO: 62) and LST-S3-14 (SEQ ID NO: 67) was rare and did not show any tissue or tumor specificity. Consistent with Northern blot analyses, the RT-PCR results on antigen LAT-S1-A-10A (SEQ ID NO: 78) suggested that its expression is high in lung, colon, stomach and small intestine tissues, including lung and colon tumors, whereas its expression was low or undetectable in other tissues.

A total of 2002 cDNA fragments isolated in lung subtractions I, II and III, described above, were colony PCR amplified and their mRNA expression levels in lung tumor, normal lung, and various other normal and tumor tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Seventeen non-redundant cDNA clones showed over-expression in lung

squamous tumors, with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or 10-fold less compared to lung squamous tumors. The determined cDNA sequences for the clone L513S are provided in SEQ ID NO: 87 and 88; those for L514S are provided in SEQ ID NO: 89 and 90; those for L516S in SEQ ID NO: 91 and 92; that for L517S in SEQ ID NO: 93; that for L519S in SEQ ID NO: 94; those for L520S in SEQ ID NO: 95 and 96; those for L521S in SEQ ID NO: 97 and 98; that for L522S in SEQ ID NO: 99; that for L523S in SEQ ID NO: 100; that for L524S in SEQ ID NO: 101; that for L525S in SEQ ID NO: 102; that for L526S in SEQ ID NO: 103; that for L527S in SEQ ID NO: 104; that for L528S in SEQ ID NO: 105; that for L529S in SEQ ID NO: 106; and those for L530S in SEQ ID NO: 107 and 108. Additionally, the full-length cDNA sequence for L530S is provided in SEQ ID NO: 151, with the corresponding amino acid sequence being provided in SEQ ID NO: 152. L530S shows homology to a splice variant of a p53 tumor suppressor homologue, p63. The cDNA sequences of 7 known isoforms of p63 are provided in SEQ ID NO: 331-337, with the corresponding amino acid sequences being provided in SEQ ID NO: 338-344, respectively.

Due to polymorphisms, the clone L531S appears to have two forms. A first determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 109, with the corresponding amino acid sequence being provided in SEQ ID NO: 110. A second determined full-length cDNA sequence for L531S is provided in SEQ ID NO: 111, with the corresponding amino acid sequence being provided in SEQ ID NO: 112. The sequence of SEQ ID NO: 111 is identical to that of SEQ ID NO: 109, except that it contains a 27 bp insertion. Similarly, L514S has two alternatively spliced forms; the first variant cDNA is listed as SEQ ID NO: 153, with the corresponding amino acid sequence being provided in SEQ ID NO: 155. The full-length cDNA for the second variant form of L514S is provided in SEQ ID NO: 154, with the corresponding amino acid sequence being provided in SEQ ID NO: 156.

Full length cloning for L524S (SEQ ID NO: 101) yielded two variants (SEQ ID NO: 163 and 164) with the corresponding amino acid sequences of SEQ ID

NO: 165 and 166, respectively. Both variants have been shown to encode parathyroid hormone-related peptide.

Attempts to isolate the full-length cDNA for L519S, resulted in the isolation of the extended cDNA sequence provided in SEQ ID NO: 173, which contains
5 a potential open reading frame. The amino acid sequence encoded by the sequence of SEQ ID NO: 173 is provided in SEQ ID NO: 174. Additionally, the full-length cDNA sequence for the clone of SEQ ID NO: 100 (known as L523S), a known gene, is provided in SEQ ID NO: 175, with the corresponding amino acid sequence being provided in SEQ ID NO: 176. In further studies, a full-length cDNA sequence for
10 L523S was isolated from a L523S-positive tumor cDNA library by PCR amplification using gene specific primers designed from the sequence of SEQ ID NO: 175. The determined full-length cDNA sequence is provided in SEQ ID NO: 347. The amino acid sequence encoded by this sequence is provided in SEQ ID NO: 348. This protein sequence differs from the previously published protein sequence at two amino acid
15 positions, namely at positions 158 and 410.

Comparison of the sequences of L514S and L531S (SEQ ID NO: 87 and 88, and 109, respectively) with those in the gene bank, as described above, revealed no significant homologies to known sequences. The sequences of L513S, L516S, L517S, L519S, L520S and L530S (SEQ ID NO: 87 and 88, 91 and 92, 93, 94, 95 and 96, 107
20 and 108, respectively) were found to show some homology to previously identified ESTs. The sequences of L521S, L522S, L523S, L524S, L525S, L526S, L527S, L528S and L529S (SEQ ID NO: 97 and 98, 99, 99, 101, 102, 103, 104, 105, and 106, respectively) were found to represent known genes. The determined full-length cDNA sequence for L520S is provided in SEQ ID NO: 113, with the corresponding amino
25 acid sequence being provided in SEQ ID NO: 114. Subsequent microarray analysis showed L520S to be overexpressed in breast tumors in addition to lung squamous tumors.

Further analysis demonstrated that L529S (SEQ ID NO: 106 and 115), L525S (SEQ ID NO: 102 and 120) and L527S (SEQ ID NO: 104) are cytoskeletal
30 components and potentially squamous cell specific proteins. L529S is connexin 26, a gap junction protein. It was found to be highly expressed in one lung squamous tumor,

referred to as 9688T, and moderately over-expressed in two others. However, lower level expression of connexin 26 is also detectable in normal skin, colon, liver and stomach. The over-expression of connexin 26 in some breast tumors has been reported and a mutated form of L529S may result in over-expression in lung tumors. L525S is
5 plakophilin 1, a desmosomal protein found in plaque-bearing adhering junctions of the skin. Expression levels for L525S mRNA was highly elevated in three out of four lung squamous tumors tested, and in normal skin. L527S has been identified as keratin 6 isoform, type II 58 Kd keratin and cytokeratin 13, and shows over-expression in squamous tumors and low expression in normal skin, breast and colon tissues. Keratin
10 and keratin-related genes have been extensively documented as potential markers for lung cancer including CYFRA2.1 (Pastor, A., et al, *Eur. Respir. J.*, 10:603-609, 1997). L513S (SEQ ID NO: 87 and 88) shows moderate over-expression in several tumor tissues tested, and encodes a protein that was first isolated as a pemphigus vulgaris antigen.

15 L520S (SEQ ID NO: 95 and 96) and L521S (SEQ ID NO: 97 and 98) are highly expressed in lung squamous tumors, with L520S being up-regulated in normal salivary gland and L521S being over-expressed in normal skin. Both belong to a family of small proline rich proteins and represent markers for fully differentiated squamous cells. L521S has been described as a specific marker for lung squamous tumor (Hu, R.,
20 et al, *Lung Cancer*, 20:25-30, 1998). L515S (SEQ ID NO: 162) encodes IGF- β 2 and L516S is an aldose reductase homologue. Both are moderately expressed in lung squamous tumors and in normal colon. Notably, L516S (SEQ ID NO: 91 and 92) is up-regulated in metastatic tumors but not primary lung adenocarcinoma, an indication of its potential role in metatasis and a potential prognostic marker. L522S (SEQ ID NO: 99)
25 is moderately over-expressed in lung squamous tumors with minimum expression in normal tissues. L522S has been shown to belong to a class IV alcohol dehydrogenase, ADH7, and its expression profile suggests it is a squamous cell specific antigen. L523S (SEQ ID NO: 100) is moderately over-expressed in lung squamous tumor, human pancreatic cancer cell lines and pancreatic cancer tissues, suggesting this gene may be a
30 shared antigen between pancreatic and lung squamous cell cancer.

L524S (SEQ ID NO: 101) is over-expressed in the majority of squamous tumors tested and is homologous with parathyroid hormone-related peptide (PTHrP), which is best known to cause humoral hypercalcaemia associated with malignant tumors such as leukemia, prostate and breast cancer. It is also believed that PTHrP is most commonly associated with squamous carcinoma of lung and rarely with lung adenocarcinoma (Davidson, L.A., et al, *J. Pathol.*, 178: 398-401, 1996). L528S (SEQ ID NO: 105) is highly over-expressed in two lung squamous tumors with moderate expression in two other squamous tumors, one lung adenocarcinoma and some normal tissues, including skin, lymph nodes, heart, stomach and lung. It encodes the NMB gene that is similar to the precursor of melanocyte specific gene Pmel17, which is reported to be preferentially expressed in low-metastatic potential melanoma cell lines. This suggests that L528S may be a shared antigen in both melanoma and lung squamous cell carcinoma. L526S (SEQ ID NO: 103) was overexpressed in all lung squamous cell tumor tissues tested and has been shown to share homology with a gene (ATM) in which a mutation causes ataxia telangiectasia, a genetic disorder in humans causing a predisposition to cancer, among other symptoms. ATM encodes a protein that activates a p53 mediated cell-cycle checkpoint through direct binding and phosphorylation of the p53 molecule. Approximately 40% of lung cancers are associated with p53 mutations, and it is speculated that over-expression of ATM is a result of compensation for loss of p53 function, but it is unknown whether over-expression is the cause of result of lung squamous cell carcinoma. Additionally, expression of L526S (ATM) is also detected in a metastatic but not lung adenocarcinoma, suggesting a role in metastasis.

Expression of L523S (SEQ ID NO: 175), was examined by real time RT-PCR as described above. In a first study using a panel of lung squamous tumors, L523S was found to be expressed in 4/7 lung squamous tumors, 2/3 head and neck squamous tumors and 2/2 lung adenocarcinomas, with low level expression being observed in skeletal muscle, soft palate and tonsil. In a second study using a lung adenocarcinoma panel, expression of L523S was observed in 4/9 primary adenocarcinomas, 2/2 lung pleural effusions, 1/1 metastatic lung adenocarcinomas and 2/2 lung squamous tumors, with little expression being observed in normal tissues.

Expression of L523S in lung tumors and various normal tissues was also examined by Northern blot analysis, using standard techniques. In a first study, L523S was found to be expressed in a number of lung adenocarcinomas and squamous cell carcinomas, as well as normal tonsil. No expression was observed in normal lung. In a
5 second study using a normal tissue blot (referred to as HB-12) from Clontech, no expression was observed in brain, skeletal muscle, colon, thymus, spleen, kidney, liver, small intestine, lung or PBMC, although there was strong expression in placenta.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF LUNG TUMOR POLYPEPTIDES

10

BY PCR-BASED SUBTRACTION

Eight hundred and fifty seven clones from a cDNA subtraction library, containing cDNA from a pool of two human lung squamous tumors subtracted against eight normal human tissue cDNAs including lung, PBMC, brain, heart, kidney, liver, pancreas, and skin, (Clontech, Palo Alto, CA) were derived and submitted to a first
15 round of PCR amplification. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the P7-Adv vector (Clontech, Palo Alto, CA) and transformed into DH5 α *E. coli* (Gibco, BRL). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer
20 Model 373A.

One hundred and sixty two positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the EMBL and GenBank databases, as described above, revealed no significant homologies to 13 of these clones, hereinafter referred to as Contigs 13, 16, 17, 19, 22, 24, 29, 47, 49, 56-59. The determined cDNA
25 sequences for these clones are provided in SEQ ID NO: 125, 127-129, 131-133, 142, 144, 148-150, and 157, respectively. Contigs 1, 3-5, 7-10, 12, 11, 15, 20, 31, 33, 38, 39, 41, 43, 44, 45, 48, 50, 53, 54 (SEQ ID NO: 115-124, 126, 130, 134-141, 143, 145-147, respectively) were found to show some degree of homology to previously identified DNA sequences. Contig 57 (SEQ ID NO: 149) was found to represent the clone L519S

(SEQ ID NO: 94) disclosed in US. Patent Application No. 09/123,912, filed July 27, 1998. To the best of the inventors' knowledge, none of these sequences have been previously shown to be differentially over-expressed in lung tumors.

mRNA expression levels for representative clones in lung tumor tissues,
5 normal lung tissues (n=4), resting PBMC, salivary gland, heart, stomach, lymph nodes, skeletal muscle, soft palate, small intestine, large intestine, bronchial, bladder, tonsil, kidney, esophagus, bone marrow, colon, adrenal gland, pancreas, and skin (all derived from human) were determined by RT-PCR as described above. Expression levels using microarray technology, as described above, were examined in one sample of each tissue
10 type unless otherwise indicated.

Contig 3 (SEQ ID NO: 116) was found to be highly expressed in all head and neck squamous cell tumors tested (17/17), and expressed in the majority (8/12) of lung squamous tumors, (high expression in 7/12, moderate in 2/12, and low in 2/12), while showing negative expression for 2/4 normal lung tissues and low expression in
15 the remaining two samples. Contig 3 showed moderate expression in skin and soft palate, and lowered expression levels in resting PBMC, large intestine, salivary gland, tonsil, pancreas, esophagus, and colon. Contig 11 (SEQ ID NO: 124) was found to be expressed in all head and neck squamous cell tumors tested (17/17), with high levels of expression being seen in 14/17 tumors, and moderately levels of expression being seen
20 in 3/17 tumors. Additionally, high expression was seen in 3/12 lung squamous tumors and moderate expression in 4/12 lung squamous tumors. Contig 11 was negative for 3/4 normal lung samples, with the remaining sample having only low expression. Contig 11 showed low to moderate reactivity to salivary gland, soft palate, bladder, tonsil, skin, esophagus, and large intestine. Contig 13 (SEQ ID NO: 125) was found to be expressed
25 in all head and neck squamous cell tumors tested (17/17), with high expression in 12/17, and moderate expression in 5/17. Contig 13 was expressed in 7/12 lung squamous tumors, with high expression in 4/12 and moderate expression in three samples. Analysis of normal lung samples showed negative expression for 2/4 and low to moderate expression in the remaining two samples. Contig 13 showed low to
30 moderate reactivity to resting PBMC, salivary gland, bladder, pancreas, tonsil, skin, esophagus, and large intestine, as well as high expression in soft palate. Subsequent

full-length cloning efforts revealed that contig 13 (also known as L761P) maps to the 3' untranslated region of the hSec10p gene. The full-length sequence for this gene is set forth in SEQ ID NO: 368, and encodes the protein set forth in SEQ ID NO: 369.

Contig 16 (SEQ ID NO: 127) was found to be moderately expressed in
5 several head and neck squamous cell tumors (6/17) and one lung squamous tumor, while showing no expression in any normal lung samples tested. Contig 16 showed low reactivity to resting PBMC, large intestine, skin, salivary gland, and soft palate. Contig 17 (SEQ ID NO: 128) was shown to be expressed in all head and neck squamous cell tumors tested (17/17) (highly expressed in 5/17, and moderately expressed in 12/17).
10 Determination of expression levels in lung squamous tumors showed one tumor sample with high expression and 3/12 with moderate levels. Contig 17 was negative for 2/4 normal lung samples, with the remaining samples having only low expression. Additionally, low level expression was found in esophagus and soft palate. Contig 19 (SEQ ID NO: 129) was found to be expressed in most head and neck squamous cell
15 tumors tested (11/17); with two samples having high expression levels, 6/17 showing moderate expression, and low expression being found in 3/17. Testing in lung squamous tumors revealed only moderate expression in 3/12 samples. Expression levels in 2/4 of normal lung samples were negative, the two other samples having only low expression. Contig 19 showed low expression levels in esophagus, resting PBMC,
20 salivary gland, bladder, soft palate and pancreas.

Contig 22 (SEQ ID NO: 131), was shown to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in four of these samples, moderate expression in 6/17, and low expression in 3/17. Expression levels in lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with
25 negative expression in two normal lung samples and low expression in two other samples (n=4). Contig 22 showed low expression in skin, salivary gland and soft palate. Similarly, Contig 24 (SEQ ID NO: 132) was found to be expressed in most head and neck squamous cell tumors tested (13/17) with high expression in three of these samples, moderate expression in 6/17, and low expression in 4/17. Expression levels in
30 lung squamous tumors were found to be moderate to high for 3/12 tissues tested, with negative expression for three normal lung samples and low expression in one sample

(n=4). Contig 24 showed low expression in skin, salivary gland and soft palate. Contig 29 (SEQ ID NO: 133) was expressed in nearly all head and neck squamous cell tumors tested (16/17): highly expressed in 4/17, moderately expressed in 11/17, with low expression in one sample. Also, it was moderately expressed in 3/12 lung squamous tumors, while being negative for 2/4 normal lung samples. Contig 29 showed low to moderate expression in large intestine, skin, salivary gland, pancreas, tonsil, heart and soft palate. Contig 47 (SEQ ID NO: 142) was expressed in most head and neck squamous cell tumors tested (12/17): moderate expression in 10/17, and low expression in two samples. In lung squamous tumors, it was highly expressed in one sample and moderately expressed in two others (n=13). Contig 47 was negative for 2/4 normal lung samples, with the remaining two samples having moderate expression. Also, Contig 47 showed moderate expression in large intestine, and pancreas, and low expression in skin, salivary gland, soft palate, stomach, bladder, resting PBMC, and tonsil.

Contig 48 (SEQ ID NO: 143) was expressed in all head and neck squamous cell tumors tested (17/17): highly expressed in 8/17 and moderately expressed in 7/17, with low expression in two samples. Expression levels in lung squamous tumors were high to moderate in three samples (n=13). Contig 48 was negative for one out of four normal lung samples, the remaining showing low or moderate expression. Contig 48 showed moderate expression in soft palate, large intestine, pancreas, and bladder, and low expression in esophagus, salivary gland, resting PBMC, and heart. Contig 49 (SEQ ID NO: 144) was expressed at low to moderate levels in 6/17 head and neck squamous cell tumors tested. Expression levels in lung squamous tumors were moderate in three samples (n=13). Contig 49 was negative for 2/4 normal lung samples, the remaining samples showing low expression. Moderate expression levels in skin, salivary gland, large intestine, pancreas, bladder and resting PBMC were shown, as well as low expression in soft palate, lymph nodes, and tonsil. Contig 56 (SEQ ID NO: 148) was expressed in low to moderate levels in 3/17 head and neck squamous cell tumors tested, and in lung squamous tumors, showing low to moderate levels in three out of thirteen samples. Notably, low expression levels were detected in one adenocarcinoma lung tumor sample (n=2). Contig 56 was negative for

3/4 normal lung samples, and showed moderate expression levels in only large intestine, and low expression in salivary gland, soft palate, pancreas, bladder, and resting PBMC. Contig 58, also known as L769P, (SEQ ID NO: 150) was expressed at moderate levels in 11/17 head and neck squamous cell tumors tested and low expression in one
5 additional sample. Expression in lung squamous tumors showed low to moderate levels in three out of thirteen samples. Contig 58 was negative for 3/4 normal lung samples, with one sample having low expression. Moderate expression levels in skin, large intestine, and resting PBMC were demonstrated, as well as low expression in salivary gland, soft palate, pancreas, and bladder. Contig 59 (SEQ ID NO: 157) was expressed in
10 some head, neck, and lung squamous tumors. Low level expression of Contig 59 was also detected in salivary gland and large intestine.

The full-length cDNA sequence for Contig 22, also referred to as L763P, is provided in SEQ ID NO: 158, with the corresponding amino acid sequence being provided in SEQ ID NO: 159. Real-time RT-PCR analysis of L763P revealed that it is
15 highly expressed in 3/4 lung squamous tumors as well as 4/4 head and neck squamous tumors, with low level expression being observed in normal brain, skin, soft pallet and trachea. Subsequent database searches revealed that the sequence of SEQ ID NO: 158 contains a mutation, resulting in a frameshift in the corresponding protein sequence. A second cDNA sequence for L763P is provided in SEQ ID NO: 345, with the
20 corresponding amino acid sequence being provided in SEQ ID NO: 346. The sequences of SEQ ID NO: 159 and 346 are identical with the exception of the C-terminal 33 amino acids of SEQ ID NO: 159.

The full-length cDNA sequence incorporating Contigs 17, 19, and 24, referred to as L762P, is provided in SEQ ID NO: 160, with the corresponding amino
25 acid sequence being provided in SEQ ID NO: 161. Further analysis of L762P has determined it to be a type I membrane protein and two additional variants have been sequenced. Variant 1 (SEQ ID NO: 167, with the corresponding amino acid sequence in SEQ ID NO: 169) is an alternatively spliced form of SEQ ID NO: 160 resulting in deletion of 503 nucleotides, as well as deletion of a short segment of the expressed
30 protein. Variant 2 (SEQ ID NO: 168, with the corresponding amino acid sequence in SEQ ID NO: 170) has a two nucleotide deletion at the 3' coding region in comparison

to SEQ ID NO: 160, resulting in a secreted form of the expressed protein. Real-time RT-PCR analysis of L762P revealed that is over-expressed in 3/4 lung squamous tumors and 4/4 head & neck tumors, with low level expression being observed in normal skin, soft pallet and trachea.

5 An epitope of L762P was identified as having the sequence KPGHWTYTLNNTTHHSLQALK (SEQ ID NO: 382), which corresponds to amino acids 571-590 of SEQ ID NO:161.

 The full-length cDNA sequence for contig 56 (SEQ ID NO: 148), also referred to as L773P, is provided in SEQ ID NO: 171, with the amino acid sequence in
10 SEQ ID NO: 172. L773P was found to be identical to dihydroxyl dehydrogenase at the 3' portion of the gene, with divergent 5' sequence. As a result, the 69 N-terminal amino acids are unique. The cDNA sequence encoding the 69 N-terminal amino acids is provided in SEQ ID NO: 349, with the N-terminal amino acid sequence being provided in SEQ ID NO: 350. Real-time PCR revealed that L773P is highly expressed in lung
15 squamous tumor and lung adenocarcinoma, with no detectable expression in normal tissues. Subsequent Northern blot analysis of L773P demonstrated that this transcript is differentially over-expressed in squamous tumors and detected at approximately 1.6 Kb in primary lung tumor tissue and approximately 1.3 Kb in primary head and neck tumor tissue.

20 Subsequent microarray analysis has shown Contig 58, also referred to as L769S (SEQ ID NO: 150), to be overexpressed in breast tumors in addition to lung squamous tumors.

EXAMPLE 4

ISOLATION AND CHARACTERIZATION OF LUNG TUMOR POLYPEPTIDES

25 BY PCR-BASED SUBTRACTION

 Seven hundred and sixty clones from a cDNA subtraction library, containing cDNA from a pool of two human lung primary adenocarcinomas subtracted against a pool of nine normal human tissue cDNAs including skin, colon, lung, esophagus, brain, kidney, spleen, pancreas and liver, (Clontech, Palo Alto, CA) were

derived and submitted to a first round of PCR amplification. This library (referred to as ALT-1) was subjected to a second round of PCR amplification, following the manufacturer's protocol. The expression levels of these 760 cDNA clones in lung tumor, normal lung, and various other normal and tumor tissues, were examined using
5 microarray technology (Incyte, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence
10 intensity was measured. This intensity correlates with the hybridization intensity.. A total of 118 clones, of which 55 were unique, were found to be over-expressed in lung tumor tissue, with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or at significantly lower
15 levels. One of these clones, having the sequence as provided in SEQ ID NO:420 (clone #19014), shows homology to a previously identified clone, L773P. Clone L773P has the full-length cDNA sequence provided in SEQ ID NO:171 and the amino acid sequence provided in SEQ ID NO:172 The isolation of clone #19014 is also described in co-pending U.S. Patent application 09/285,479, filed April 2, 1999.

20

EXAMPLE 5

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-
25 Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support is carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides are precipitated in cold methyl-t-

butyl-ether. The peptide pellets are then dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure
5 fractions, the peptides are characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 6

PREPARATION OF ANTIBODIES AGAINST LUNG CANCER ANTIGENS

Polyclonal antibodies against the lung cancer antigens L514S, L528S,
10 L531S, L523 and L773P (SEQ ID NO: 155, 225, 112, 176 and 171, respectively) were prepared as follows.

Rabbits were immunized with recombinant protein expressed in and purified from *E. coli* as described below. For the initial immunization, 400 µg of antigen combined with muramyl dipeptide (MDP) was injected subcutaneously (S.C.).
15 Animals were boosted S.C. 4 weeks later with 200 µg of antigen mixed with incomplete Freund's Adjuvant (IFA). Subsequent boosts of 100 µg of antigen mixed with IFA were injected S.C. as necessary to induce high antibody titer responses. Serum bleeds from immunized rabbits were tested for antigen-specific reactivity using ELISA assays with purified protein. Polyclonal antibodies against L514S, L528S, L531S, L523S and
20 L773P were affinity purified from high titer polyclonal sera using purified protein attached to a solid support.

Immunohistochemical analysis using polyclonal antibodies against L514S was performed on a panel of 5 lung tumor samples, 5 normal lung tissue samples and normal colon, kidney, liver, brain and bone marrow. Specifically, tissue samples
25 were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize L514S immunoreactivity. L514S was found to be highly expressed in lung tumor tissue with little or no expression being observed in

normal lung, brain or bone marrow. Light staining was observed in colon (epithelial crypt cells positive) and kidney (tubules positive). Staining was seen in normal liver but no mRNA has been detected in this tissue making this result suspect.

Using the same procedure, immunohistochemical analysis using
5 polyclonal antibodies against L528S demonstrated staining in lung tumor and normal lung samples, light staining in colon and kidney, and no staining in liver and heart.

Immunohistochemical analysis using polyclonal antibodies against
L531S demonstrated staining in lung tumor samples, light membrane staining in most normal lung samples, epithelial staining in colon, tubule staining in kidney, ductal
10 epithelial staining in liver and no staining in heart.

Immunohistochemical analysis using polyclonal antibodies against
L523S demonstrated staining in all lung cancer samples tested but no staining in normal lung, kidney, liver, colon, bone marrow or cerebellum.

Generation of polyclonal anti-sera against L762P (SEQ ID NO: 169 and
15 170) was performed as follows. 400 micrograms of lung antigen was combined with 100 micrograms of muramyl dipeptide (MDP). An equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed until an emulsion was formed. Rabbits were injected subcutaneously (S.C.). After four weeks the animals were injected S.C. with 200 micrograms of antigen mixed with an equal volume of IFA.
20 Every four weeks animals were boosted with 100 micrograms of antigen. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

Characterization of polyclonal antisera was carried out as follows.
Ninety-six well plates were coated with antigen by incubating with 50 microliters
25 (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hrs. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS and 50 microliters of diluted sera was added to each well and incubated at room temperature for 30 min.
Plates were washed as described above before addition of 50 microliters of goat anti-
30 rabbit horse radish peroxidase (HRP) at a 1:10000 dilution and incubation at room temperature for 30 min. Plates were washed as described above and 100µl of TMB

Microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 μ l 1N H₂SO₄ and read immediately at 450 nm. Antisera showed strong reactivity to antigen L762P.

- 5 Immunohistochemical analysis using polyclonal antibodies against L762P demonstrated staining in all lung cancer samples tested, some light staining in the bronchiole epithelium of normal lung, tubule staining in kidney, light epithelial staining in colon and no staining in heart or liver.

- In order to evaluate L773P protein expression in various tissues, immunohistochemistry (IHC) analysis was performed using an affinity purified L773P polyclonal antibody. Briefly, tissue samples were fixed in formalin solution for 12-24 hrs and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody was added to each section for 25 minutes at indicated concentrations followed by 25 minute incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize L773P expression. Slides were counterstained with hematoxylin to visualize cell nuclei. Using this approach, L773P protein was detected in 6/8 lung tumors, 4/6 normal lung samples (very light staining in some cases), 1/1 kidney samples (very light staining), 0/1 heart samples, 1/1 colon samples (very light staining) and 0/1 liver samples.

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EXAMPLE 7

PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

Immunogenic peptides from the lung cancer antigen L762P (SEQ ID NO: 161) for HLA-A2/K^b-restricted CD8⁺ T cells were identified as follows.

The location of HLA-A2 binding peptides within the lung cancer antigen L762P (SEQ ID NO: 161) was predicted using a computer program which predicts peptides sequences likely to be to HLA-A*0201 by fitting to the known peptide binding motif for HLA-A*0201 (Rupert *et al.* (1993) *Cell* 74:929; Rammensee *et al.* (1995) *Immunogenetics* 41:178-228). A series of 19 synthetic peptides corresponding to a selected subset of the predicted HLA-A*0201 binding peptides was prepared as described above.

Mice expressing the transgene for human HLA A2/K^b (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with the synthetic peptides, as described by Theobald *et al.*, *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995, with the following modifications. Mice were immunized with 50µg of L726P peptide and 120µg of an I-A^b binding peptide derived from hepatitis B virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared. Cells were then resuspended at 7×10^6 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2×10^{-5} M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) L762P peptide- (5µg/ml) and 10mg/ml B₂-microglobulin- (3 µg/ml) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). After six days, cells (5×10^5 /ml) were restimulated with 2.5×10^6 /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman *et al.*, *Science* 258:815-818, 1992) and 5×10^6 /ml irradiated (3000 rads) A2/K^b-transgenic spleen feeder cells. Cells were cultured in the presence of 10U/ml IL-2. Cells were restimulated on a weekly basis as described, in preparation for cloning the line.

Peptide-specific cell lines were cloned by limiting dilution analysis with irradiated (20,000 rads) L762P peptide-pulsed EL4 A2Kb tumor cells (1×10^4 cells/well) as stimulators and irradiated (3000 rads) A2/K^b-transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 10U/ml IL-2. On day 7, cells were restimulated as before. On day 14, clones that were growing were isolated and maintained in culture.

Cell lines specific for the peptides L762P-87 (SEQ ID NO: 226; corresponding to amino acids 87-95 of SEQ ID NO: 161), L762P-145 (SEQ ID NO: 227; corresponding to amino acids 145-153 of SEQ ID NO: 161), L762P-585 (SEQ ID NO: 228; corresponding to amino acids 585-593 of SEQ ID NO: 161), L762P-425 (SEQ ID NO: 229; corresponding to amino acids 425-433 of SEQ ID NO: 161), L762P(10)-424 (SEQ ID NO: 230; corresponding to amino acids 424-433 of SEQ ID NO: 161) and L762P(10)-458 (SEQ ID NO: 231; corresponding to amino acids 458-467 of SEQ ID NO: 161) demonstrated significantly higher reactivity (as measured by percent specific lysis) against L762P peptide-pulsed EL4-A2/K^b tumor target cells than control peptide-pulsed EL4-A2/K^b tumor target cells.

EXAMPLE 8

IDENTIFICATION OF CD4 IMMUNOGENIC T CELL EPITOPES DERIVED FROM THE LUNG CANCER ANTIGEN L762P

CD4 T cell lines specific for the antigen L762P (SEQ ID NO: 161) were generated as follows.

A series of 28 overlapping peptides were synthesized that spanned approximately 50% of the L762P sequence. For priming, peptides were combined into pools of 4-5 peptides, pulsed at 20 micrograms/ml into dendritic cells for 24 hours. The dendritic cells were then washed and mixed with positively selected CD4⁺ T cells in 96 well U-bottomed plates. Forty cultures were generated for each peptide pool. Cultures were restimulated weekly with fresh dendritic cells loaded with peptide pools. Following a total of 3 stimulation cycles, cells were rested for an additional week and tested for specificity to antigen presenting cells (APC) pulsed with peptide pools using interferon-gamma ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool or an irrelevant peptide were used as APC. T cell lines that appeared to specifically recognize L762P peptide pools both by cytokine release and proliferation were identified for each pool. Emphasis was placed on identifying T cells with proliferative responses. T cell lines that demonstrated either both L762P-specific cytokine secretion and proliferation, or strong proliferation

alone were further expanded to be tested for recognition of individual peptides from the pools, as well as for recognition of recombinant L762P. The source of recombinant L762P was *E. coli*, and the material was partially purified and endotoxin positive. These studies employed 10 micrograms of individual peptides, 10 or 2 micrograms of an irrelevant peptide, and 2 or 0.5 micrograms of either L762P protein or an irrelevant, equally impure, *E. coli* generated recombinant protein. Significant interferon-gamma production and CD4 T cell proliferation was induced by a number of L762P-derived peptides in each pool. The amino acid sequences for these peptides are provided in SEQ ID NO: 232-251. These peptides correspond to amino acids 661-680, 676-696, 526-545, 874-893, 811-830, 871-891, 856-875, 826-845, 795-815, 736-755, 706-725, 706-725, 691-710, 601-620, 571-590, 556-575, 616-635, 646-665, 631-650, 541-560 and 586-605, respectively, of SEQ ID NO: 161.

CD4 T cell lines that demonstrated specificity for individual L762P-derived peptides were further expanded by stimulation with the relevant peptide at 10 micrograms/ml. Two weeks post-stimulation, T cell lines were tested using both proliferation and IFN-gamma ELISA assays for recognition of the specific peptide. A number of previously identified T cells continued to demonstrate L762P-peptide specific activity. Each of these lines was further expanded on the relevant peptide and, following two weeks of expansion, tested for specific recognition of the L762P-peptide in titration experiments, as well as for recognition of recombinant *E. coli*-derived L762P protein. For these experiments, autologous adherent monocytes were pulsed with either the relevant L762P-derived peptide, an irrelevant mammaglobin-derived peptide, recombinant *E. coli*-derived L762P (approx. 50% pure), or an irrelevant *E. coli*-derived protein. The majority of T cell lines were found to show low affinity for the relevant peptide, since specific proliferation and IFN-gamma ratios dramatically decreased as L762P peptide was diluted. However, four lines were identified that demonstrated significant activity even at 0.1 micrograms/ml peptide. Each of these lines (referred to as A/D5, D/F5, E/A7 and E/B6) also appeared to specifically proliferate in response to the *E. coli*-derived L762P protein preparation, but not in response to the irrelevant protein preparation. The amino acid sequences of the L762P-derived peptides recognized by these lines are provided in SEQ ID NO: 234, 249, 236 and 245,

respectively. No protein specific IFN-gamma was detected for any of the lines. Lines A/D5, E/A7 and E/B6 were cloned on autologous adherent monocytes pulsed with the relevant peptide at 0.1 (A/D5 and E/A7) or 1 (D/F5) microgram/ml. Following growth, clones were tested for specificity for the relevant peptide. Numerous clones specific for
 5 the relevant peptide were identified for lines A/D5 and E/A7.

EXAMPLE 9

PROTEIN EXPRESSION OF LUNG TUMOR-SPECIFIC ANTIGENS

a) Expression of L514S in *E. coli*

The lung tumor antigen L514S (SEQ ID NO: 89) was subcloned into the
 10 expression vector pE32b at NcoI and NotI sites, and transformed into *E. coli* using standard techniques. The protein was expressed from residues 3-153 of SEQ ID NO: 89. The expressed amino acid sequence and the corresponding DNA sequence are provided in SEQ ID NO: 252 and 253, respectively.

b) Expression of L762P

15 Amino acids 32-944 of the lung tumor antigen L762P (SEQ ID NO: 161), with a 6X His Tag, were subcloned into a modified pET28 expression vector, using kanamycin resistance, and transformed into BL21 CodonPlus using standard techniques. Low to moderate levels of expression were observed. The determined DNA sequence of the L762P expression construct is provided in SEQ ID NO: 254.

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EXAMPLE 10

IDENTIFICATION OF MHC CLASS II RESTRICTING ALLELE FOR L762P PEPTIDE-SPECIFIC .RESPONSES

A panel of HLA mismatched antigen presenting cells (APC) were used to identify the MHC class II restricting allele for the L762P-peptide specific responses
 25 of CD4 T cell clones derived from lines that recognized L762P peptide and recombinant protein. Clones from two lines, AD-5 and EA-7, were tested as described below. The

AD-5 derived clones were found to be restricted by the HLA-DRB-1101 allele, and an EA-7 derived clone was found to be restricted by the HLA DRB-0701 or DQB1-0202 allele. Identification of the restriction allele allows targeting of vaccine therapies using the defined peptide to individuals that express the relevant class II allele. Knowing the relevant restricting allele will also enable clinical monitoring for responses to the defined peptide since only individuals that express the relevant allele will be monitored.

CD4 T cell clones derived from line AD-5 and EA-7 were stimulated on autologous APC pulsed with the specific peptide at 10 µg/ml, and tested for recognition of autologous APC (from donor D72) as well as against a panel of APC partially matched with D72 at class II alleles. Table 2 shows the HLA class typing of the APC tested. Adherent monocytes (generated by 2 hour adherence) from four different donors, referred to as D45, D187, D208, and D326, were used as APC in these experiments. Autologous APC were not included in the experiment. Each of the APC were pulsed with the relevant peptide (5a for AD-5 and 3e for 3A-7) or the irrelevant mammoglobin peptide at 10 µg/ml, and cultures were established for 10,000 T cells and about 20,000 APC/well. As shown in Table 3, specific proliferation and cytokine production could be detected only when partially matched donor cells were used as APC. Based on the MHC typing analysis, these results strongly suggest that the restricting allele for the L762-specific response of the AD-5 derived clones is HLA-DRB-1101 and for the EA-7 derived clone the restricting allele is HLA DRB-0701 or DQB1-0202.

Table 2 - HLA Typing of APC

DONOR	DR	DR	DQ	DQ
D72	B1-1101	B1-0701	B1-0202	B1-0301
D45	-3	-15	B1-0201	B1-0602
D187	-4	-15	-1	-7
D208	B1-1101	B1-0407	-3	-3
D326	B1-0301	B1-0701	B1-0202	B1-0201

Table 3 - L762P Peptide Responses Map to HLA DR Alleles

			AD-5																								EA-7	
			A11		B10		C10		C11		E6		F1		F9		G8		G9		G10		G12					
Donor	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN	ProI	γ -IFN				
D72 DR-0701, -1101, DQ-0202, -7	46		31		34		24		31		40		55		45		43		91		10							
D45 DR-3,-15, DQ-1, -0201	32	1.7	5.5	1.2	3.3	1	1.0	1.5	1.1	1.1	1.6	1.1	1.4	1.3	0.2	1.1	1.1	1.1	1.2	1.5	0.8	1.1						
D187 DR-4, -15, DQ-1,-7	1.4	1.2	1.3	1	1.4	1.1	1.4	1.7	1.0	1.1	1.4	1.2	1.2	1.1	0.9	1	1.0	1	1.0	1.6	0.5	1						
D208 DR-4, -1101, DQ-3	138	13	38	5.4	18.8	10	14.6	4.6	15.3	6.1	45.9	8.6	73.3	14.1	38.0	7.7	174.3	16.1	113.6	19.6	0.8	1						
D326 DR-3, -0701, DQ-0202	0.7	4	0.3	1	0.3	1.4	1.0	2	0.8	1.1	0.3	1.1	0.7	1.1	0.6	1.2	0.4	1	1.2	5	14.1	6.8						

EXAMPLE 11

FUSION PROTEINS OF N-TERMINAL AND C-TERMINAL PORTIONS OF L763P

In another embodiment, a *Mycobacterium tuberculosis*-derived polynucleotide, referred to as Ra12, is linked to at least an immunogenic portion of a polynucleotide of this invention. Ra12 compositions and methods for their use in enhancing expression of heterologous polynucleotide sequences are described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). Surprisingly, it was discovered that a 14 KD C-terminal fragment of the MTB32A coding sequence expresses at high levels on its own and remains as a soluble protein throughout the purification process. Moreover, this fragment may enhance the immunogenicity of heterologous antigenic polypeptides with which it is fused. This 14 KD C-terminal fragment of the MTB32A is referred to herein as Ra12 and represents a fragment comprising some or all of amino acid residues 192 to 323 of MTB32A.

Recombinant nucleic acids which encode a fusion polypeptide comprising a Ra12 polypeptide and a heterologous lung tumor polypeptide of interest, can be readily constructed by conventional genetic engineering techniques. Recombinant nucleic acids are constructed so that, preferably, a Ra12 polynucleotide sequence is located 5' to a selected heterologous lung tumor polynucleotide sequence. It may also be appropriate to place a Ra12 polynucleotide sequence 3' to a selected heterologous polynucleotide sequence or to insert a heterologous polynucleotide sequence into a site within a Ra12 polynucleotide sequence.

In addition, any suitable polynucleotide that encodes a Ra12 or a portion or other variant thereof can be used in constructing recombinant fusion polynucleotides comprising Ra12 and one or more lung tumor polynucleotides disclosed herein.

Preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide.

Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Two specific embodiments of fusions between Ra12 and antigens of the present invention are described in this example.

A. N-Terminal Portion of L763P

A fusion protein of full-length Ra12 and the N-terminal portion of L763P (referred to as L763P-N; amino acid residues 1-130 of SEQ ID NO: 159) was expressed as a single recombinant protein in *E. coli*. The cDNA for the N-terminal portion was obtained by PCR with a cDNA for the full length L763P and primers L763F3 (5' CGGCGAATTCATGGATTGGGGGACGCTGC; SEQ ID NO: 383) and 1763RV3 (5' CGGCCTCGAGTCACCCCTCTATCCGAACCTTCTGC; SEQ ID NO: 384). The PCR product with expected size was recovered from agarose gel, digested with restriction enzymes *EcoRI* and *XhoI*, and cloned into the corresponding sites in the expression vector pCRX1. The sequence for the fusion of full-length of Ra12 and L763P-N was confirmed by DNA sequencing. The determined cDNA sequence is provided in SEQ ID NO:351, with the corresponding amino acid sequence being provided in SEQ ID NO: 352).

B. C-Terminal Portion of L763P

A fusion protein of full-length Ra12 and the C-terminal portion of L763P (referred to as L763P-C; amino acid residues 100-262 of SEQ ID NO: 159) was expressed as a single recombinant protein in *E. coli*. The cDNA of the C-terminal portion of L763P was obtained by PCR with a cDNA for the full length of L763P and primers L763F4 (5' CGGCGAATTCCACGAACCACTCGCAAGTTCAG; SEQ ID NO: 385) and L763RV4 (5' CGGCTCGAG-TTAGCTTGGGCCTGTGATTGC; SEQ ID NO: 386). The PCR product with expected size was recovered from agarose gel, digested with restriction enzymes EcoRI and XhoI, and cloned into the corresponding sites in the expression vector pCRX1. The sequence for the fusion of full-length Ra12 and L763P-C was confirmed by DNA sequencing. The determined DNA sequence is provided in SEQ ID NO:353, with the corresponding amino acid sequence being provided in SEQ ID NO: 354.

The recombinant proteins described in this example are useful for the preparation of vaccines, for antibody therapeutics, and for diagnosis of lung tumors.

EXAMPLE 12

EXPRESSION IN *E. COLI* OF L762P HIS TAG FUSION PROTEIN

PCR was performed on the L762P coding region with the following primers:

Forward primer starting at amino acid 32.

PDM-278 5'ggagtacagcttcaagacaatggg 3' (SEQ ID NO:355) Tm 57°C.

Reverse primer including natural stop codon after amino acid 920, creating EcoRI site

PDM-280 5'ccatgggaattcattataataattttgttcc 3' (SEQ ID NO:356) Tm 55°C.

The PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The

correct construct was confirmed by DNA sequence analysis and then transformed into BL21 (DE3) pLys S and BL21 (DE3) CodonPlus RIL expression hosts.

The protein sequence of expressed recombinant L762P is shown in SEQ ID NO:357, and the DNA sequence is shown in SEQ ID NO:358.

EXAMPLE 13

EXPRESSION IN *E. COLI* OF A L773PA HIS TAG FUSION PROTEIN

The L773PA coding region (encoding amino acids 2-71 of SEQ ID NO: 172) was PCR amplified using the following primers:

Forward primer for L773PA starting at amino acid 2:

PDM-299 5'tggcagccctcttctcaagtggc 3' (SEQ ID NO:359) Tm63°C.

Reverse primer for L773PA creating artificial stop codon after amino acid 70:

PDM-355 5'cgccagaattcatcaacaaatctgtagcacc 3' (SEQ ID NO:360) Tm62°C.

The resulting PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and transformed into BL21 (DE3) pLys S and BL21 (DE3) CodonPlus RIL expression hosts.

The protein sequence of expressed recombinant L773PA is shown in SEQ ID NO:361, and the DNA sequence is shown in SEQ ID NO:362.

EXAMPLE 14

IDENTIFICATION OF EPITOPES DERIVED FROM LUNG TUMOR SPECIFIC POLYPEPTIDES

A series of peptides from the L773P amino acid sequence (SEQ ID NO: 172) were synthesized and used in *in vitro* priming experiments to generate peptide-specific CD4 T cells. These peptides were 20-mers that overlapped by 15 amino acids and corresponded to amino acids 1-69 of the L773P protein. This region has been demonstrated to be tumor-specific. Following three *in vitro* stimulations, CD4 T cell

lines were identified that produced IFN γ in response to the stimulating peptide but not the control peptide. Some of these T cell lines demonstrated recognition of recombinant L773P and L773PA (tumor-specific region) proteins.

To perform the experiments, a total of eleven 20-mer peptides (SEQ ID NO: 363, 365 and 387-395) overlapping by 15 amino acids and derived from the N-terminal tumor-specific region of L773P (corresponding to amino acids 1-69 of SEQ ID NO:172) were generated by standard procedures. Dendritic cells were derived from PBMC of a normal donor using GM-CSF and IL-4 by standard protocol. Purified CD4 T cells were generated from the same donor as the dendritic cells using MACS beads and negative selection of PBMCs. Dendritic cells were pulsed overnight with the individual 20-mer peptides at a concentration of 10 μ g/ml. Pulsed dendritic cells were washed and plated at 1×10^4 /well of a 96-well U-bottom plates, and purified CD4 cells were added at 1×10^5 well. Cultures were supplemented with 10 ng/ml IL-6 and 5 ng/ml IL-12, and incubated at 37°C. Cultures were re-stimulated as above on a weekly basis using as APC dendritic cells generated and pulsed as above, supplemented with 5 ng/ml IL-7 and 10 μ g/ml IL-2. Following 3 *in vitro* stimulation cycles, cell lines (each corresponding to one well) were tested for cytokine production in response to the stimulating peptide vs. an irrelevant peptide.

A small number of individual CD4 T cell lines (9/528) demonstrated cytokine release (IFN γ) in response to the stimulating peptide but not to control peptide. The CD4 T cell lines that demonstrated specific activity were restimulated on the appropriate L773P peptide and reassayed using autologous dendritic cells pulsed with 10 μ g/ml of the appropriate L773P peptide, an irrelevant control peptide, recombinant L773P protein (amino acids 2-364, made in *E. coli*), recombinant L773PA (amino acids 2-71, made in *E. coli*), or an appropriate control protein (L3E, made in *E. coli*). Three of the nine lines tested (1-3C, 1-6G, and 4-12B) recognized the appropriate L773P peptide as well as recombinant L773P and L773PA. Four of the lines tested (4-8A, 4-8E, 4-12D, and 4-12E) recognized the appropriate L773P peptide only. Two of the lines tested (5-6F and 9-3B) demonstrated non-specific activity.

These results demonstrate that the peptide sequences MWQPLFFKWLLSCCPGSSQI (amino acids 1-20 of SEQ ID NO: 172; SEQ ID NO:363) and GSSQIAAAASTQPEDDINTQ (amino acids 16-35 of SEQ ID NO: 172;

SEQ ID NO: 365) may represent naturally processed epitopes of L773P, which are capable of stimulating human class II MHC-restricted CD4 T cell responses.

In subsequent studies, the above epitope mapping experiment was repeated using a different donor. Again, some of the resulting T cell lines were found to respond to peptide and recombinant protein. An additional peptide was found to be naturally processed. Specifically, purified CD4 cells were stimulated on a total of eleven 20-mer peptides overlapping by 15 amino acids (SEQ ID NO: 363, 387, 388, 365 and 389-395, respectively). The priming was carried out as described above, except that a peptide concentration of 0.5 ug/mL rather than 10 ug/mL was employed. In the initial screen of the cell lines 9 of the 528 lines released at least a three-fold greater level of IFN-gamma with stimulating peptide vs. control peptide. These 9 lines were restimulated on the appropriate peptide and then tested on dendritic cells pulsed with a titration of appropriate peptide (10 ug/mL, 1 ug/mL and 0.1 ug/mL), and 10 ug/mL of a control peptide. Six of the 9 lines recognized recombinant L773P as well as peptide. The six lines referred to as 1-1E, 1-2E, 1-4H, 1-6A, 1-6G and 2-12B recognized L773PA and the appropriate peptide. These results demonstrate that the peptides of SEQ ID NO: 363 and 387 represent naturally processed epitopes of L773P.

Using the procedures described above, CD4+ T cell responses were generated from PBMC of normal donors using dendritic cells pulsed with overlapping 20-mer peptides (SEQ ID NO: 396-419) spanning the L523S polypeptide sequence (SEQ ID NO: 176). A number of CD4+ T cells demonstrated reactivity with the priming peptides as well as with L523S recombinant protein, with the dominant reactivity of these lines being within the peptides 4, 7 and 21 (SEQ ID NO: 399, 402 and 416; corresponding to amino acids 30-39, 60-79 and 200-219, respectively, of SEQ ID NO: 176).

Epitopes within the scope of the invention include epitopes restricted by other class II MHC molecules. In addition, variants of the peptide can be produced wherein one or more amino acids are altered such that there is no effect on the ability of the peptides to bind to MHC molecules, no effect on their ability to elicit T cell responses, and no effect on the ability of the elicited T cells to recognize recombinant protein.

EXAMPLE 15

SURFACE EXPRESSION OF L762P AND ANTIBODY EPITOPES THEREOF

Rabbits were immunized with full-length histidine-tagged L762P protein generated in *E. coli*. Sera was isolated from rabbits and screened for specific recognition of L762P in ELISA assays. One polyclonal serum, referred to as 2692L, was identified that specifically recognized recombinant L762P protein. The 2692L anti-L762P polyclonal antibodies were purified from the serum by affinity purification using L762P affinity columns. Although L762P is expressed in a subset of primary lung tumor samples, expression appears to be lost in established lung tumor cell lines. Therefore, to characterize surface expression of L762P, a retrovirus construct that expresses L762P was used to transduce primary human fibroblasts as well as 3 lung tumor cell lines (522-23, HTB, and 343T). Transduced lines were selected and expanded to examine L762P surface expression by FACS analysis. For this analysis, non-transduced and transduced cells were harvested using cell dissociation medium, and incubated with 10-50 micrograms/ml of either affinity purified anti-L762P or irrelevant antisera. Following a 30 minute incubation on ice, cells were washed and incubated with a secondary, FITC conjugated, anti rabbit IgG antibody as above. Cells were washed, resuspended in buffer with Propidium Iodide (PI) and examined by FACS using an Excalibur fluorescence activated cell sorter. For FACS analysis, PI-positive (i.e. dead/permeabilized cells) were excluded. The polyclonal anti-L762P sera specifically recognized and bound to the surface of L762P-transduced cells but not the non-transduced counterparts. These results demonstrate that L762P is localized to the cell surface of both fibroblasts as well as lung tumor cells.

To identify the peptide epitopes recognized by 2692L, an epitope mapping approach was pursued. A series of overlapping 19-21 mers (5 amino acid overlap) was synthesized that spanned the C terminal portion of L762P (amino acids 481-894 of SEQ ID NO: 161). In an initial experiment peptides were tested in pools. Specific reactivity with the L762P antiserum was observed with pools A, B, C, and E. To identify the specific peptides recognized by the antiserum, flat bottom 96 well microtiter plates were coated with individual peptides at 10 microgram/ml for 2 hours at

37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 5% (w/v) milk for 2 hours at 37 °C, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit anti-L762P serum 2692L was added at 200 or 20 ng/well to triplicate wells in PBST and incubated overnight at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti rabbit IgG (H+L)Affinipure F(ab') fragment at 1:2,000 for 60 minutes. Plates were then washed, and incubated in tetramethyl benzidine substrate. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450/570 nm using an ELISA plate reader.

The resulting data, presented in Table 4 below, demonstrates that the L762P antisera recognized at least 6 distinct peptide epitopes from the 3' half of L762P.

Table 4
ELISA activity (OD 450-570)

Peptide (starting amino acid of L762P)	pool	200 ng polyclonal serum	20 ng polyclonal serum
A (481)	A	1.76	1.0
B (495)	A	0.14	.06
C (511)	E	0.47	0.18
D (526)	E	0.11	0.09
E (541)	A	0.11	0.04
F (556)	A	0.04	0.02
G (571)	A	0.06	0.02
H (586)	B	0.1	0.03
I (601)	B	0.25	0.06
J (616)	B	0.1	0.03
K (631)	E	0.1	0.08
L (646)	B	0.28	0.12
M (661)	B	0.14	0.03
N (676)	C	0.12	0.1
O (691)	C	1.1	0.23
P (706)	C	0.1	0.03
Q (721)	C	0.11	0.05
R (736)	E	0.12	0.04
S (751)	C	0.15	0.06
U (781)	D	0.12	0.06
V (795)	F	0.07	0.05
X (826)	D	0.1	0.03
Y (841)	D	0.17	0.07
Z (856)	D	0.16	0.08
AA (871)	F	0.17	0.05
BB (874)	F	0.14	0.11
No peptide		0.15	0.045

Individual peptides were identified from each of the pools, and additionally a weak reactivity was identified with peptide BB from pool F. The relevant peptide epitopes are summarized in the Table 5 below. The amino acid sequences for peptides BB, O, L, I, A and C are provided in SEQ ID NO: 376-381, respectively, with the corresponding cDNA sequences being provided in SEQ ID NO: 373, 370, 372, 374, 371 and 375, respectively.

Table 5

ELISA activity
(OD 450-570)

Peptide	Nucleotides of L762P	Amino acids of L762P	Sequence	pool	200 ng	20 ng
A	1441-1500	481-500	SRISSGTGDIFQQHIQLEST	A	1.76	1.0
C	1531-1590	511-530	KNTVTVDNTVGNDTMFLVTW	E	0.47	0.18
I	1801-1860	601-620	AVPPATVEAFVERDSLHFP	B	0.25	0.06
L	1936-1955	646-665	PETGDPVTLRLDDGAGADV	B	0.28	0.12
O	2071-2130	691-710	VNHSPSISTPAHSIPGSHAMIL	C	1.1	0.23
BB	2620-2679	874-893	LQSAVSNIAQAPLFIPPNSD	F	0.14	0.11
None	-	-	-	-	0.15	0.05

EXAMPLE 16**DETECTION OF ANTIBODIES AGAINST LUNG TUMOR ANTIGENS IN PATIENT SERA**

Antibodies specific for the lung tumor antigens L773PA (SEQ ID NO:361), L514S (SEQ ID NO:155 and 156), L523S (SEQ ID NO:176), L762P (SEQ ID NO:161) and L763P (SEQ ID NO:159) were shown to be present in effusion fluid or sera of lung cancer patients but not in normal donors. More specifically, the presence of antibodies against L773PA, L514S, L523S, L762P and L763P in effusion fluid obtained from lung cancer patients and in sera from normal donors was detected by ELISA using recombinant proteins and HRP-conjugated anti-human Ig. Briefly, each protein (100 ng) was coated in 96-well plate at pH 9.5. In parallel, BSA (bovine serum albumin) was also coated as a control protein. The signals ([S], absorbance measured at 405 nm) against BSA ([N]) were determined. The results of these studies are shown in Table 6, wherein - represents $[S]/[N] < 2$; +/- represents $[S]/[N] > 2$; ++ represents $[S]/[N] > 3$; and +++ represents $[S]/[N] > 5$.

Table 6

Detection of Antibodies Against Lung Tumor Antigens

	L514S	L523S	L762P	L763P	L773PA
Effusion fluid					
#1	+++	++	++	-	++
#2	-	-	+/-	++	+/-
#3	-	-	-	-	+/-
#4	+/-	++	+/-	-	+/-
#5	+/-	+++	+/-	+/-	++
#7	-	+/-	-	-	+/-
#8	-	+++	-	-	++
#10	-	++	+/-	+/-	-
#11	+/-	++	++	-	++
#12	+++	+/-	-	+/-	+/-
#13	-	+/-	-	-	+/-
#14	-	+++	+/-	+/-	++
#15	+/-	++	+/-	-	++
#17	-	+/-	-	-	+/-
#18	-	++	-	-	-
#19	-	+/-	-	-	+/-
#20	+/-	+/-	+/-	-	+/-
Normal sera					
#21	-	+/-	-	-	-
#22	-	-	-	-	-
#23	-	-	-	-	+/-
#24	-	+/-	-	-	-
#25	+/-	+/-	-	-	+/-

Using Western blot analyses, antibodies against L523S were found to be present in 3 out of 4 samples of effusion fluid from lung cancer patients, with no L523S antibodies being detected in the three samples of normal sera tested.

EXAMPLE 17

EXPRESSION IN *E. COLI* OF A L514S HIS TAG FUSION PROTEIN

PCR was performed on the L514S-13160 coding region with the following primers:

Forward primer PDM-278 5' cacactagtgtccgcgtggcggcctac 3' (SEQ ID NO:421) Tm 67°C.

Reverse primer PDM-280 5' catgagaattcatcacatgcccttgaaggctccc 3'
(SEQ ID NO:422) T_m 66°C.

The PCR conditions were as follows:

10µl 10X Pfu buffer
1.0µl 10mM dNTPs
2.0µl 10µM each primer
83µl sterile water
1.5µl Pfu DNA polymerase (Stratagene, La Jolla, CA)
50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 66°C for 15 seconds, 72°C for 1 minute with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into BL21 CodonPlus (Stratagene, La Jolla, CA) cells for expression.

The amino acid sequence of expressed recombinant L514S is shown in SEQ ID NO:423, and the DNA coding region sequence is shown in SEQ ID NO:424.

EXAMPLE 18

EXPRESSION IN *E. COLI* OF A L523S HIS TAG FUSION PROTEIN

PCR was performed on the L523S coding region with the following primers:

Forward primer PDM-414 5' aacaaactgtatatcggaacctcagcgagaa 3' (SEQ ID NO:425) T_m 62°C.

Reverse primer PDM-415 5' ccatagaattcattacttcggtcttgactgagg 3' (SEQ ID NO:426) T_m 62°C.

The PCR conditions were as follows:

10µl 10X Pfu buffer
1.0µl 10mM dNTPs

2.0 μ l 10 μ M each primer

83 μ l sterile water

1.5 μ l Pfu DNA polymerase (Stratagene, La Jolla, CA)

50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 62°C for 15 seconds, 72°C for 4 minutes with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into BL21 CodonPlus (Stratagene, La Jolla, CA) cells for expression.

The amino acid sequence of expressed recombinant L523S is shown in SEQ ID NO:427, and the DNA coding region sequence is shown in SEQ ID NO:428.

EXAMPLE 19

EXPRESSION IN *E. COLI* OF A L762PA HIS TAG FUSION PROTEIN

PCR was performed on the L762PA coding region (L762PA is missing the signal sequence, the C-terminal transmembrane domain and the cytoplasmic tail) with the following primers:

Forward primer PDM-278 5'ggagtacagcttcaagacaatggg 3' (SEQ ID NO:355) Tm 57°C.

Reverse primer PDM-279 5'ccatggaattcattatttcaatataagataatctc 3' (SEQ ID NO:429) TM56°C.

The PCR conditions were as follows:

10 μ l 10X Pfu buffer

1.0 μ l 10mM dNTPs

2.0 μ l 10 μ M each primer

83 μ l sterile water

1.5 μ l Pfu DNA polymerase (Stratagene, La Jolla, CA)

50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 55°C for 15 seconds, 72°C for 5 minutes with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into BL21 pLys S (Novagen, Madison, WI) cells for expression.

The amino acid sequence of expressed recombinant L762PA is shown in SEQ ID NO:430, and the DNA coding region sequence is shown in SEQ ID NO:431.

EXAMPLE 20

EXPRESSION IN *E. COLI* OF A L773P HIS TAG FUSION PROTEIN

PCR was performed on the L773P coding region with the following primers:

Forward primer PDM-299 5' tggcagccctcttcttcaagtggc 3' (SEQ ID NO:359) Tm 63°C.

Reverse primer PDM-300 5' cgctgctcgagtcattaatattcatcagaaaatgg 3' (SEQ ID NO:432) TM 63°C.

The PCR conditions were as follows:

10µl 10X Pfu buffer

1.0µl 10mM dNTPs

2.0µl 10µM each primer

83µl sterile water

1.5µl Pfu DNA polymerase (Stratagene, La Jolla, CA)

50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 63°C for 15 seconds, 72°C for 2 minutes 15 seconds with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with EcoRI restriction enzyme, gel purified and then cloned into pPDM His, a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The

correct construct was confirmed by DNA sequence analysis and then transformed into BL21 pLys S (Novagen, Madison, WI) and BL21 CodonPlus (Stratagene, La Jolla, CA) cells for expression.

The amino acid sequence of expressed recombinant L773P is shown in SEQ ID NO:433, and the DNA coding region sequence is shown in SEQ ID NO:434.

EXAMPLE 21

CLONING AND SEQUENCING OF A T-CELL RECEPTOR CLONE FOR THE LUNG SPECIFIC ANTIGEN L762P

T cell receptor (TCR) alpha and beta chains from a CD4 T cell clone specific for the lung specific antigen L762P were cloned and sequence. Basically, total mRNA from 2×10^6 cells from CTL clone 4H6 was isolated using Trizol reagent and cDNA was synthesized using Ready-to go kits (Pharmacia). To determine Valpha and Vbeta sequences of this clone, a panel of Valpha and Vbeta subtype specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vbeta sequence that corresponded to the Vbeta8 subfamily and a Valpha sequence that corresponded to the Valpha8 subfamily. To clone the full TCR alpha and beta chains from clone 4H6, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows:

forward primer for TCR Valpha8 5'
ggatccgccgccaccatgacatccattcgagctgta 3' (SEQ ID NO:435; has a BamHI site inserted);

Kozak reverse primer for TCR Valpha8 (antisense) 5'
gtcgactcagctggaccacagccgcag 3' (SEQ ID NO:436; has a SalI site inserted plus the TCR alpha constant sequence);

forward primer for TCR Vbeta8 (sense) 5'
ggatccgccgccaccatggactcctggaccttctgct 3' (SEQ ID NO:437; has a BamHI site inserted); and

Kozak reverse primer for TCR Vbeta 5' gtcgactcagaaatcctttctcttgac 3' (SEQ ID NO:438; has a Sall site inserted plus the TCR beta constant sequence). Standard 35 cycle RT-PCR reactions were established using the cDNA synthesized from the CTL clone and the above primers utilizing the proofreading thermostable polymerase, PWO (Roche). The resultant PCR band, about 850 bp for Valpha and about 950 for Vbeta, was ligated into a PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids having full-length alpha and beta chains were identified.. Large scale preparations of the corresponding plasmids were generated, and these plasmids were sequenced. The Valpha sequence (SEQ ID NO:439) was shown by nucleotide sequence alignment to be homologous to Valpha8.1, while the Vbeta sequence (SEQ ID NO:440) was shown by nucleotide sequence alignment to be homologous to Vbeta8.2.

EXAMPLE 22

RECOMBINANT EXPRESSION OF FULL LENGTH L762P IN MAMMALIAN CELLS

Full length L762P cDNA was subcloned into the mammalian expression vectors VR1012 and pCEP4 (Invitrogen). Both expression vectors had previously been modified to contain a FLAG epitope tag. These constructs were transfected into HEK293 and CHL-1 cells (ATCC) using Lipofectamine 2000 reagent (Gibco). Briefly, both the HEK and CHL-1 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 4µl of Lipofectamine 2000 was added to 100µl of DMEM containing no FBS and incubated for 5 minutes at room temperature. The Lipofectamine/DMEM mixture was then added to 1µg of L762P Flag/pCEP4 or L762P Flag/VR1012 plasmid DNA resuspended in 100µl DMEM and incubated for 15 minutes at room temperature. The Lipofectamine/DNA mix was then added to the HEK293 and CHL-1 cells and incubated for 48-72 hours at 37°C with 7% CO₂. Cells were rinsed with PBS, then collected and pelleted by centrifugation. L762P expression was detected in the transfected HEK293 and CHL-1 cell lysates by Western blot analysis and was detected on the surface of transfected HEK cells by flow cytometry analysis.

For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000 rpm for 5 minutes at 4°C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. The protein was transferred to nitrocellulose and probed using 1 µg/ml purified anti-L762P rabbit polyclonal sera (lot #690/73) or non-diluted anti-L762P mAb 153.20.1 supernatant. Blots were revealed using either goat anti-rabbit Ig coupled to HRP or goat anti-mouse Ig coupled to HRP followed by incubation in ECL substrate.

For flow cytometric analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA +Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of purified anti-L762P polyclonal sera (lot #690/73) or a 1:2 dilution of anti-L762P mAb 153.20.1 supernatant. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of goat anti-rabbit Ig(H+L)-FITC or goat anti-mouse Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. After 3 washes, the cells were resuspended in staining buffer containing propidium iodide (PI), a vital stain that allows for the exclusion of permeable cells, and analyzed by flow cytometry.

EXAMPLE 23

GENERATION OF POLYCLONAL ANTIBODIES TO LUNG TUMOR ANTIGENS

Three lung antigens, L523S (SEQ ID NO:176), L763P (SEQ ID NO:159) and L763 peptide #2684 (SEQ ID NO:441), were expressed and purified for use in antibody generation.

L523S and L763P were expressed in an *E. coli* recombinant expression system and grown overnight in LB Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml of 2x YT with the appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the optical density of the culture reached 0.4-0.6 at 560 nanometers, the cells were

induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation.

The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run through a french press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein.

For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8M urea or 6M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes to 1 hour at room temperature with continuous agitation.

After incubation, the resin and protein mixture was poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin, in this case Hi-Prep Q (Biorad), was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool.

The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The release criteria were purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino

terminal protein sequence, and endotoxin level was determined by the Limulus (LAL) assay. The proteins were then put in vials after filtration through a 0.22-micron filter and the antigens were frozen until needed for immunization.

The L763 peptide #2684 was synthesized and conjugated to KLH and froze until needed for immunization.

The polyclonal antisera were generated using 400 micrograms of each lung antigen combined with 100 micrograms of muramyl dipeptide (MDP). An equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed and injected subcutaneously (S.C.) into a rabbit. After four weeks, the rabbit was S.C. boosted with 200 micrograms of antigen mixed with an equal volume of IFA. Thereafter the rabbit was I.V. boosted with 100 micrograms of antigen. The animal was bled seven days following each boost. The blood was then incubated at 4°C for 12-24 hours followed by centrifugation to generate the sera.

The polyclonal antisera were characterized using 96 well plates coated with antigen and incubated with 50 microliters (typically 1 microgram/microliter) of the polyclonal antisera at 4°C for 20 hours. Basically, 250 microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.1% Tween. The rabbit sera were diluted in PBS/0.1% Tween/0.1% BSA. 50 microliters of diluted sera was added to each well and incubated at room temperature for 30 minutes. The plates were washed as described above, and then 50 microliters of goat anti-rabbit horseradish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 minutes.

The plates were washed as described above, and 100 microliters of TMB Microwell Peroxidase Substrate was added to each well. Following a 15-minute incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H₂SO₄ and read immediately at 450 nm. All the polyclonal antibodies showed immunoreactivity to the appropriate antigen. Tables 7-9 show the antibody reactivity of rabbit antisera in serial dilution to the three lung antigens, L523S, L763P and L763 peptide #2684. The first column shows the antibody dilutions. The columns "Pre-immune sera" indicate ELISA data for two experiments using pre-immune sera. These results are averaged in the fourth column. The columns "anti-

L523S, L763P or #2684" indicate ELISA data for two experiments using sera from rabbits immunized as described in this Example, using the respective antigen, referred to as either L523S, L763P or #2684 in the tables.

Table 7

Antibody dilution	Pre-immune sera (1)	Pre-immune sera (2)	Average	Anti-L523S (1)	Anti-L523S (2)	Average
1:1000	0.14	0.14	0.14	2.36	2.37	2.37
1:2000	0.12	0.10	0.11	2.29	2.23	2.26
1:4000	0.10	0.09	0.10	2.11	2.17	2.14
1:8000	0.09	0.09	0.09	1.98	2.00	1.99
1:16000	0.09	0.09	0.09	1.73	1.76	1.75
1:32000	0.09	0.09	0.09	1.35	1.40	1.37
1:64000	0.09	0.11	0.10	0.94	0.98	0.96
1:128000	0.09	0.08	0.08	0.61	0.61	0.61
1:256000	0.08	0.08	0.08	0.38	0.38	0.38
1:512000	0.09	0.08	0.08	0.24	0.25	0.25
1:1024000	0.08	0.08	0.08	0.17	0.17	0.17
1:2048000	0.08	0.08	0.08	0.14	0.13	0.13

Table 8

Antibody dilution	Pre-immune sera (1)	Pre-immune sera (2)	Average	Anti-L763P (1)	Anti-L763P (2)	Average
1:1000	0.09	0.11	0.10	1.97	1.90	1.93
1:2000	0.07	0.07	0.07	1.86	1.84	1.85
1:4000	0.06	0.06	0.06	1.82	1.81	1.81
1:8000	0.06	0.06	0.06	1.83	1.81	1.82
1:16000	0.06	0.05	0.06	1.79	1.74	1.76
1:32000	0.06	0.06	0.06	1.56	1.51	1.53
1:64000	0.06	0.05	0.05	1.35	1.34	1.35
1:128000	0.05	0.05	0.05	1.01	0.98	0.99
1:256000	0.06	0.05	0.05	0.69	0.70	0.70
1:512000	0.06	0.05	0.05	0.47	0.44	0.46
1:1024000	0.06	0.05	0.06	0.27	0.27	0.27
1:2048000	0.05	0.05	0.05	0.16	0.15	0.16

Table 9

Antibody dilution	Pre-immune sera (1)	Pre-immune sera (2)	Average	Anti-#2684 (1)	Anti-#2684 (2)	Average
1:1000	0.07	0.07	0.07	2.10	2.00	2.05
1:2000	0.07	0.06	0.06	1.95	1.96	1.95
1:4000	0.06	0.06	0.06	1.77	1.82	1.79
1:8000	0.06	0.06	0.06	1.79	1.81	1.80
1:16000	0.06	0.06	0.06	1.54	1.50	1.52
1:32000	0.06	0.06	0.06	1.27	1.20	1.24
1:64000	0.06	0.06	0.06	0.85	0.82	0.83
0	0.06	0.06	0.06	0.06	0.06	0.06

Tables 10-12 show the affinity purification of the respective antibodies to the three lung antigens, L523S, L763P and L763 peptide #2684.

Table 10

Antibody conc. (µg/ml)	Affinity pure (salt peak)	Affinity pure (salt peak)	Average	Affinity pure (acid peak)	Affinity pure (acid peak)	Average
1.0	2.38	2.35	2.36	2.25	2.31	2.28
0.5	2.24	2.22	2.23	2.19	2.18	2.18
0.25	2.05	2.09	2.07	2.01	2.03	2.02
0.13	1.70	1.81	1.75	1.74	1.74	1.74
0.063	1.44	1.44	1.44	1.43	1.38	1.40
0.031	1.05	1.05	1.05	0.99	0.99	0.99
0.016	0.68	0.67	0.68	0.65	0.64	0.64
0.0078	0.43	0.42	0.42	0.39	0.39	0.39
0.0039	0.27	0.26	0.27	0.24	0.26	0.25
0.0020	0.18	0.20	0.19	0.19	0.18	0.19
0.0010	0.13	0.14	0.13	0.13	0.14	0.13
0.00	0.11	0.12	0.11	0.10	0.12	0.11

Table 11

Antibody dilution	Affinity pure	Affinity pure	Average
1:1000	1.64	1.77	1.70
1:2000	1.59	1.76	1.68
1:4000	1.48	1.62	1.55
1:8000	1.35	1.43	1.39
1:16000	1.09	1.19	1.14
1:32000	0.81	0.89	0.85
1:64000	0.55	0.58	0.56
1:128000	0.31	0.35	0.33
1:256000	0.18	0.20	0.19
1:512000	0.11	0.12	0.11
1:1024000	0.07	0.07	0.07
1:2048000	0.06	0.06	0.06

Table 12

Antibody conc. (µg/ml)	Affinity pure	Affinity pure	Average
1.0	2.00	2.02	2.01
0.5	2.01	1.93	1.97
0.25	1.84	1.83	1.84
0.13	1.80	1.83	1.81
0.06	1.39	1.60	1.50
0.03	1.33	1.35	1.34
0.02	0.94	0.93	0.94
0.00	0.06	0.06	0.06

EXAMPLE 24

FULL-LENGTH cDNA SEQUENCE ENCODING L529S

The isolation of a partial sequence (SEQ ID NO:106) for lung antigen L529S was previously provided in Example 2. This partial sequence was used as a query to identify potential full length cDNA and protein sequences by searching against publicly available databases. The predicted full-length cDNA sequence for the isolated

cloned sequence of SEQ ID NO:106 is provided in SEQ ID NO:442. The deduced amino acid sequence of the antigen encoded by SEQ ID NO:442 is provided in SEQ ID NO:443. It was previously disclosed in Example 2 that L529S shows similarity to connexin 26, a gap junction protein.

EXAMPLE 25

EXPRESSION IN MEGATERIUM OF A HISTIDINE TAG-FREE L523S FUSION PROTEIN

PCR was performed on the L523S coding region with the following primers:

Forward primer PDM-734 5' caatcaggcatgcacaacaaactgtatatcggaac 3' (SEQ ID NO:444) Tm 63°C.

Reverse primer PDM-735 5' cgtaagatcttcattactccgtcttgac 3' (SEQ ID NO:445) TM 60°C.

The PCR conditions were as follows:

10µl 10X Pfu buffer

1.0µl 10mM dNTPs

2.0µl 10µM each primer

83µl sterile water

1.5µl Pfu DNA polymerase (Stratagene, La Jolla, CA)

50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 62°C for 15 seconds, 72°C for 4 minute with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with SphI and BglII restriction enzymes, gel purified and then cloned into pMEG-3, which had been digested with SphI and BglII restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into Megaterium cells for expression.

The amino acid sequence of expressed recombinant L523S is shown in SEQ ID NO:446, and the DNA coding region sequence is shown in SEQ ID NO:447.

EXAMPLE 26

EXPRESSION IN *E. COLI* OF A HISTIDINE TAG-FREE L523S FUSION PROTEIN

PCR was performed on the L552S coding region with the following primers:

Forward primer PDM-733 5' cgtactagcatatgaacaaactgtatatcggaac 3'
(SEQ ID NO:448) Tm 64°C.

Reverse primer PDM-415 5' ccataagaattcattacttcgcttctgactgagg 3' (SEQ
ID NO:426) TM 62°C.

The PCR conditions were as follows:

10µl 10X Pfu buffer

1.0µl 10mM dNTPs

2.0µl 10µM each primer

83µl sterile water

1.5µl Pfu DNA polymerase (Stratagene, La Jolla, CA)

50ng DNA

96°C for 2 minutes, 96°C for 20 seconds, 62°C for 15 seconds, 72°C for
4 minute with 40 cycles and then 72°C for 4 minutes.

The PCR product was digested with NdeI and EcoRI restriction
enzymes, gel purified and then cloned into pPDM, a modified pET28 vector, which had
been digested with NdeI and EcoRI restriction enzymes. The correct construct was
confirmed by DNA sequence analysis and then transformed into BLR pLys S and HMS
174 pLys S cells for expression.

The amino acid sequence of expressed recombinant L523S is shown in
SEQ ID NO:449, and the DNA coding region sequence is shown in SEQ ID NO:450.

EXAMPLE 27

EPITOPE-ANALYSIS OF L514S AND L523S-SPECIFIC ANTIBODIES

Peptides of candidate antigens can be used for the evaluation of antibody
responses in both preclinical and clinical studies. These data allow one to further

confirm the antibody response against a certain candidate antigen. Protein-based ELISA with and without competitive peptides and peptide-based ELISA can be used to evaluate these antibody responses. Peptide ELISA is especially useful since it can further exclude the false positive of the antibody titer observed in protein-based ELISA as well as to provide the simplest assay system to test antibody responses to candidate antigens. In this example, data was obtained using both L514S- and L523S-peptides that show that individual cancer patients produce L514S- and L523S-specific antibodies. The L514S-specific antibodies recognize primarily the following epitope of L514S:

aa86-110: LGKEVRDAKITPEAFEKLGFPAAKE (SEQ ID NO:451).

This epitope is the common epitope in humans. A rabbit antibody specific for L514S recognizes two addition epitopes of L514S:

(1) aa21-45: KASDGDYYTLAVPMGDVPMDGISVA (SEQ ID NO:452)

(2) aa121-135: PDRDVLNLTQLNPKVK (SEQ ID NO:453)

It was further found that the SEQ ID NO:452 is common to both L514S isoforms, L514S-13160 and L514S-13166, whereas the other epitopes, SEQ ID NO:451 and SEQ ID NO:453, are probably specific to the isoform, L514S-13160.

The L523S-specific antibodies recognize primarily the following epitope of L523S:

aa440-460: KIAPAEAPDAKVRMVITGP (SEQ ID NO:454).

This epitope is the common epitope in humans. A rabbit antibody specific for L523S recognizes two other epitopes:

(1) aa156-175 PDGAAQQNNPLQQPRG (SEQ ID NO:455)

(2) aa326-345: RTITVKGNVETCAKAEEMEIM (SEQ ID NO:456)

In further studies, it was determined by peptide based ELISAs that eight additional epitopes of L523S were recognized by L523S-specific antibodies:

- | | | | |
|----------------|----------------------|------|----|
| (1) aa40-59 | AFVDCPDESWALKAEALS | (SEQ | ID |
| | NO:457) | | |
| (2) aa80-99: | IRKLQIRNIPPHLQWEVLDS | (SED | ID |
| | NO:458) | | |
| (3) aa160-179: | AQQNPLQQPRGRRGLGQRGS | (SEQ | ID |
| | NO:459) | | |
| (4) aa180-199: | DVHRKENAGAAEKSITILST | (SED | ID |
| | NO:460) | | |
| (5) aa320-339: | LYNPERTITVKGNVETCAKA | (SEQ | ID |
| | NO:461) | | |
| (6) aa340-359: | EEEIMKKIRESYENDIASMN | (SED | ID |
| | NO:462) | | |
| (7) aa370-389: | LNALGLFPPTSGMPPPTSGP | (SEQ | ID |
| | NO:463) | | |
| (8) aa380-399: | KIAPAEAPDAKVRMVITGP | (SED | ID |
| | NO:464) | | |

Out of these, six epitopes are common in both lung plural effusion fluid samples and in sera of lung patients. Of these six, SEQ ID NO:459 and SEQ ID NO:463 have no homology to other L523S-family proteins such as IGF-II mRNA-binding proteins 1 and 2. Accordingly, this indicates that these two peptides can be used as an assay system to determine the antibody response to L523S.

EXAMPLE 28

GENERATION OF L523S-SPECIFIC CTL LINES USING IN VITRO WHOLE-GENE PRIMING

To determine if L523S is capable of generating a CD8⁺ T cell immune response, CTLs were generated using *in vitro* whole-gene priming methodologies with tumor antigen-vaccinia infected DC (Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with the L552S tumor antigen, as determined by interferon-gamma ELISPOT analysis. Specifically, dendritic cells (DC) were

differentiated from Percoll-purified monocytes derived from PBMC of normal human donors by plastic adherence and growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following the five days of culture, the DC were infected overnight with a recombinant adenovirus that expresses L523S at a multiplicity of infection (M.O.I) of 33, 66 and 100, and matured overnight by the addition of 2 µg/ml CD40 ligand. The virus was then inactivated by UV irradiation. In order to generate a CTL line, autologous PBMC were isolated and CD8⁺ T cells were enriched for by the negative selection using magnetic beads conjugated to CD4⁺, CD14⁺, CD16⁺, CD19⁺, CD34⁺ and CD56⁺ cells. CD8⁺ T cells specific for L523S were established in round bottom 96-well plates using 10,000 L523S expressing DCs and 100,000 CD8⁺ T cells per well in RPMI supplemented with 10% human serum, 10ng/ml of IL-6 and 5ng/ml of IL-12. The cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with L523S, and the costimulatory molecule CD80 in the presence of IL-2. The cells were also stimulated with IFN-gamma to upregulate MHC Class I. The media was supplemented with 10U/ml of IL-2 at the time of stimulation as well as on days 2 and 5 following stimulation. Following three stimulation cycles, ten L523S specific CD8⁺ T cell lines were identified using interferon-gamma ELISPOT analysis that specifically produce interferon-gamma when stimulated with the L523S tumor antigen-transduced autologous fibroblasts, but not with a control antigen.

One line, 6B1, was cloned using anti-CD3 and feeder cells. The clones were tested for specificity on L523S-transduced fibroblasts. In addition, using a panel of HLA-mismatched lines transduced with a vector expressing L523S and measuring interferon-gamma production by this CTL line in an ELISPOT assay, it was determined that this clone 6B1.4B8 is restricted by HLA-A0201.

Also using transfected Cos cells, it was shown that clone 6B1.4B8 recognizes Cos cells transfected with pcDNA3 HLA A0201/L523S in an HLA-restricted and antigen specific manner.

An epitope mapping study demonstrated the clone 6B1.4B8 recognizes HLA-A201 LCL loaded with peptide pool 3 (a polypeptide corresponding to amino acid positions 33-59 of L523S).

A peptide pool breakdown study demonstrated that clone 6B1.4B8 recognizes autologous B-LCL loaded with 15-mer peptides from amino acid positions 37-55 of L523S, TGYAFVCPDESWALKAE (SEQ ID NO:465). A further peptide breakdown study demonstrated that clone 6B1.4B8 recognizes T2 cells loaded with the same 15-mer peptides.

A peptide recognition study demonstrated that clone 6B1.4B8 prefers T2 cells loaded with the peptide FVDCPESWAL (SEQ ID NO:466) which corresponds to the amino acid sequence at positions 41-51 of L523S and is encoded by the DNA sequence of SEQ ID NO:467.

EXAMPLE 29

L523S EXPRESSION IN OTHER HUMAN CANCERS

It was previously disclosed in Example 2 that L523S is expressed in lung cancers including squamous, adenocarcinoma and small cell carcinoma. To further evaluate the expression profile of this antigen an electronic expression profiling was performed. This was done by searching a L523S-specific sequence against a public EST database. Results of this profiling indicate that L523S may also be present in colon adenocarcinomas, prostate adenocarcinomas, CML, AML, Burkitt's Lymphoma, brain tumors, retinoblastomas, ovarian tumors, teratocarcinomas, uterus myosarcomas, germ cell tumors as well as pancreatic and cervical tumor cell lines.

EXAMPLE 30

IMMUNOHISTOCHEMISTRY ANALYSIS OF L523S

In order to determine which tissues express the lung tumor antigen L523S, immunohistochemistry (IHC) analysis was performed on a diverse range of tissue types. Polyclonal antibodies specific for L523S (SEQ ID NO:176) were generated as described in Example 23. IHC was performed essentially as described in Example 6. Briefly, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope

retrieval (SHIER) in 0.1 sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum in PBS for 5 minutes. The primary L523S antibody was added to each section for 25 minutes followed by a 25 minute incubation with anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/ horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

IHC analysis of L523S expression revealed that of the lung cancer tissues tested over 90% of tissue samples demonstrated high over-expression of the lung tumor antigen (10/11 adenocarcinomas and 8/9 squamous). Of the normal tissues tested, all were negative for expression of L523S, with the exception of weak staining in normal bronchus, testis, liver, and trachea.

EXAMPLE 31

GENERATION AND CHARACTERIZATION OF L762 HUMAN MONOCLONAL

ANTIBODIES

Cell supernatants from hybridoma fusions from the Xenomouse strain of transgenic mice were screened for ability to bind to L762P. All results are shown in Table 13. The primary screen was to test monoclonal supernatants for reactivity to L762P by ELISA analysis using recombinant bacterial expressed protein. We next tested the human supernatants for reactivity to surface expressed L762P by whole cell ELISA using fluorimetry analysis. Specific reactivity of the humab supernatants was confirmed by performing FACS analysis on cells transfected with either an irrelevant plasmid or a plasmid expressing L762P. FI/CFI is the relative fold increase in fluorescence intensity (FI) of the anti-L762P humab primary antibody to irrelevant human primary antibody. FI/CFI/A20 is the relative fold increase in fluorescence intensity (FI) of the anti-L762P humab primary antibody to irrelevant human primary antibody over the FI of the anti-L762P mouse monoclonal antibody 153A20.1. FI/CFI/R690 is the relative fold increase in fluorescence intensity (FI) of the anti-L762P

humab primary antibody to irrelevant human primary antibody over the FI of the anti-L762P rabbit polyclonal antibody. FACS VRL762 is the percentage of cells transfected with plasmid expressing L762P that were positive following staining with indicated monoclonal antibody. FACS VR(-) is the percentage of cells transfected with irrelevant plasmid that were positive following staining with indicated monoclonal antibody. ELISA is the O.D. values of the indicated monoclonal antibody to recombinant L762P protein. The shaded rows in Table 13 indicate those antibodies that will be further cloned and characterized.

Table 13: Human Monoclonal Antibodies Against L762P

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
R-690	4.59		1.00				
M-A20	2.88	1.00					
1.176	0.51	0.18	0.11			0.38	
1.178	1.42	0.49	0.31			0.35	
1.179	0.47	0.16	0.10			0.07	
1.180	1.50	0.52	0.33			0.26	
1.182	1.45	0.50	0.32			0.26	
1.183	0.75	0.26	0.16			0.24	
1.185	0.89	0.31	0.19			0.46	
1.186	3.45	1.20	0.75	32.68	7.14	1.22	1.93
1.187	0.36	0.13	0.08			0.06	
1.188	0.26	0.09	0.06			0.23	
1.189	0.50	0.17	0.11			0.44	
1.190	0.53	0.18	0.12			0.42	
1.191	3.12	1.08	0.68	41.44	17.90	0.86	1.29
1.192	1.91	0.66	0.42			0.12	
1.193	2.87	1.00	0.63	17.82	6.43	0.13	1.06
1.194	1.55	0.54	0.34			0.28	
1.195	0.14	0.05	0.03			0.37	
1.196	1.97	0.68	0.43			0.89	1.64
1.197	0.43	0.15	0.09			0.08	
1.198	0.54	0.19	0.12			0.33	
1.199	0.70	0.24	0.15			0.40	
1.200	2.00	0.69	0.44			0.38	1.56
1.201	1.62	0.56	0.35			0.29	
1.202	0.86	0.30	0.19			0.36	
1.203	1.56	0.27	0.18			0.14	
1.204	3.32	0.58	0.38	24.83	6.60	0.17	1.91
1.205	2.13	0.37	0.25			0.09	
1.206	0.45	0.08	0.05			0.23	
1.207	0.60	0.10	0.07			0.39	
1.208	0.12	0.02	0.01			0.36	
1.209	15.52	2.71	1.80	27.54	9.54	0.16	0.77
1.210	0.92	0.16	0.11			0.16	
1.211	2.83	0.49	0.33			0.42	
1.212	3.40	0.59	0.39	21.68	11.36	0.14	2.47
1.213	2.32	0.40	0.27			0.38	
1.214	0.80	0.14	0.09			0.34	
1.215	3.96	0.69	0.46	38.87	13.17	0.33	1.80
1.216	1.26	0.22	0.15			0.20	
1.217	1.99	0.35	0.23			0.26	

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
1.218	2.29	0.40	0.27			0.10	
1.219	0.15	0.03	0.02			0.06	
1.220	0.82	0.14	0.09			0.21	
1.221	2.29	0.40	0.27			0.12	
1.222	0.57	0.10	0.07			0.45	
1.223	0.11	0.02	0.01			0.11	
1.224	2.08	0.36	0.24			0.25	
1.225	0.95	0.17	0.11			0.22	
1.226	-0.32	-0.06	-0.04			0.06	
R-690	8.62		1.00	72.34	39.83		
M-A20	5.73	1.00		50.23	6.34		
M-A12			67.43	25.15			
M-Irr			7.74	7.35			
R-Irr			30.09	24.80			
H-Irr			25.52	39.14			
R-690	3.20		1.00				
M-A20	2.33	1.00					
1.250	0.15	0.06	0.05			0.28	
1.228	0.38	0.16	0.12			0.08	
1.229	0.39	0.17	0.12			0.44	
1.230	1.78	0.76	0.56			0.13	1.35
1.231	0.42	0.18	0.13			0.47	
1.232	0.34	0.15	0.11			0.25	
1.233	7.07	3.04	2.21	68.84	38.60	0.43	0.75
1.234	2.54	1.09	0.79	33.96	10.94	0.73	1.68
1.235	1.53	0.65	0.48			0.19	1.45
1.236	0.17	0.07	0.05			0.44	
1.237	0.35	0.15	0.11			0.06	
1.238	0.38	0.16	0.12			0.06	
1.239	0.40	0.17	0.13			0.06	
1.240	2.05	0.88	0.64	28.70	7.44	0.33	1.70
1.241	0.41	0.18	0.13			0.41	
1.242	0.52	0.23	0.16			0.05	
1.243	2.34	1.00	0.73	30.94	28.13	0.16	1.33
1.244	0.94	0.40	0.29			0.23	
1.245	0.37	0.16	0.11			0.31	
1.246	2.10	0.90	0.66	13.97	28.92	0.52	1.21
1.247	0.33	0.14	0.10			0.37	
1.248	1.80	0.77	0.56			0.76	
1.249	2.77	1.19	0.86	28.76	12.37	1.15	2.38
1.251	0.22	0.09	0.07			0.47	
1.252	1.16	0.27	0.17			0.37	
1.253	0.07	0.02	0.01			0.43	
1.254	2.05	0.48	0.30			0.14	
1.255	0.09	0.02	0.01			0.08	
1.256	1.17	0.27	0.17			0.13	
1.257	0.42	0.10	0.06			0.06	
1.258	0.48	0.11	0.07			0.40	
1.259	4.82	1.13	0.69	40.24	11.92	0.38	1.78
1.260	1.80	0.42	0.26			0.38	
2.1	2.70	0.63	0.39			0.14	1.35
2.3	0.06	0.01	0.01			0.57	
2.4	3.08	0.72	0.44	31.28	11.43	0.73	1.95
2.5	0.70	0.16	0.10			0.45	
2.6	1.26	0.29	0.18			0.22	
2.8	0.59	0.14	0.09			0.31	
2.9	7.48	1.75	1.08	45.72	17.57	0.95	1.53
2.10	0.35	0.08	0.05			0.42	
2.11	2.71	0.63	0.39			0.60	1.58

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
2.12	6.04	1.41	0.87	52.50	19.59		1.40
2.13	5.50	1.28	0.79	39.78	15.24		1.39
2.14	0.68	0.16	0.10				
2.15	6.51	1.52	0.94	49.90	15.36		1.72
2.16	4.58	1.07	0.66	28.62	13.02		1.51
2.17	8.10	1.89	1.17	48.76	18.24		3.06
R-690	6.94		1.00				
M-A20	4.28	1.00		56.40	5.00		
R-690	4.34	1.65	1.00				
M-A20	2.63	1.00	0.61				
2.18	2.29	0.87	0.53			1.27	1.95
2.20	1.85	0.70	0.43			0.52	2.75
2.21	0.09	0.03	0.02			0.40	
2.22	3.26	1.24	0.75	29.4	6.2	1.45	1.8
2.23	0.31	0.12	0.07			0.12	
2.24	1.21	0.46	0.28			0.65	
2.25	3.47	1.32	0.80	32.5	7.1	1.35	1.46
2.26	4.42	1.68	1.02	35.9	5.5	0.77	1.55
2.27	1.42	0.54	0.33			0.22	
2.28	3.00	1.14	0.69	28.6	5.4	1.21	1.26
2.29	1.41	0.53	0.32			0.58	
2.30	0.42	0.16	0.10			0.43	
2.31	0.09	0.03	0.02			0.07	
2.34	1.94	0.74	0.45			1.17	1.23
2.38	1.14	0.43	0.26			0.09	
2.39	2.50	0.95	0.57	28.2	4.8	0.78	1.14
2.40	2.02	0.77	0.46			0.47	0.99
2.41	1.16	0.44	0.27			0.08	
2.42	0.41	0.16	0.09			0.24	
2.46	2.46	0.93	0.57	16.1	4.6	1.07	1.3
2.47	1.83	0.69	0.42			0.31	1.54
2.48	2.50	0.95	0.58			1.36	1.76
2.49	0.50	0.19	0.12			0.74	
2.50	2.93	1.11	0.68	15.8	4.7	0.52	1.54
2.51	0.13	0.10	0.07			0.30	
2.52	1.11	0.79	0.56	22.1	5	1.14	1.93
2.53	1.87	1.34	0.94	29.8	7.8	0.58	2.84
2.54	1.85	1.32	0.92	15.9	8.5	0.12	2.56
2.55	0.83	0.60	0.42			0.32	
2.58	0.46	0.33	0.23			0.15	
2.60	0.99	0.71	0.50			0.35	
2.61	2.16	1.54	1.08	30.7	7.9	1.34	2.88
2.62	0.36	0.26	0.18			0.58	
2.63	0.37	0.26	0.18			0.41	
2.64	1.60	1.14	0.80	25.7	6.1	1.39	2.85
2.65	0.63	0.45	0.31			0.16	
2.66	0.08	0.06	0.04			0.06	
2.67	1.34	0.96	0.67	23.3	4.5	1.32	1.34
2.68	0.66	0.47	0.33			0.38	
2.69	2.79	1.99	1.39	46.3	9.7	1.47	1.68
2.73	1.47	1.05	0.73	28.5	7.2	1.04	1.85
2.74	1.99	1.43	1.00	39.5	19.1	1.22	1.69
2.75	1.46	1.04	0.73	25.6	7.5	0.68	1.55
2.76	1.61	1.15	0.81	27.7	7.7	0.98	1.79
2.77	1.59	1.13	0.79	27.7	4.9	1.11	1.53
2.78	1.55	1.11	0.77	13.9	8	1.51	2.64
2.79	0.33	0.24	0.16	10	5.4	0.43	
2.80	1.47	1.05	0.73	15.9	8.8	0.46	0.95
R-690	2.00	1.43	1.00				

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
M-A20	1.40	1.00		56.4	5		
R-690	3.76	3.44	1.00				
M-A20	1.09	1.00					
2.81	0.25	0.23	0.07			0.17	
2.82	0.44	0.40	0.12			0.49	
2.83	0.63	0.58	0.17			0.80	
2.84	0.13	0.12	0.04			0.55	
2.85	0.62	0.57	0.16			0.19	
2.86	0.87	0.79	0.23			0.16	
2.87	0.84	0.77	0.22			0.22	
2.89	5.88	5.37	1.56	45.9	37.9	0.07	0.73
2.90	0.23	0.21	0.06			0.60	
2.91	-0.37	-0.34	-0.10			0.43	
2.92	0.59	0.54	0.16			0.14	
2.93	0.28	0.26	0.08			0.44	
2.94	0.32	0.29	0.08			0.46	
2.95	0.39	0.36	0.10			0.51	
2.96	0.36	0.33	0.10			0.26	
2.97	1.26	1.15	0.33	36.8	14.1	1.01	0.89
2.98	0.92	0.84	0.24			0.84	
2.99	1.38	1.26	0.37	91.2	81.8	0.29	
2.100	0.94	0.86	0.25			1.40	
2.102	0.77	0.70	0.21			0.17	
2.104	1.37	1.25	0.36	10.2	7.4	0.14	
2.105	0.63	0.58	0.17			1.04	
2.106	0.79	0.72	0.21			0.84	
2.107	0.81	0.74	0.22			0.06	
2.109	0.66	1.24	0.32	19.2	6.1	0.45	0.89
2.110	1.58	3.00	0.77	36.4	14.2	0.89	1.11
2.112	0.80	1.52	0.39	28.8	6.4	1.16	1.35
2.113	0.57	1.07	0.27	31.4	10.7	0.66	1.17
2.114	0.52	0.99	0.25			0.32	
2.115	1.02	1.94	0.50	19.9	10.7	0.63	1.13
2.116	0.52	0.98	0.25			0.86	
2.118	0.19	0.36	0.09			0.06	
2.119	0.78	1.48	0.38	20.4	5.3	1.22	1.16
2.120	0.76	1.44	0.37	21.8	6	1.29	0.97
2.121	1.24	2.36	0.60	28.7	10.7	0.30	1.17
2.122	1.20	2.29	0.58	31.3	8.3	1.13	1.14
2.123	0.67	1.27	0.33	17.7	6.8	0.74	1.27
R-690	2.06	3.91	1.00				
M-A20	0.53	1.00		56.4	5		
R-690	3.51		1.00				
M-A20	2.91	1.00					
1.1	1.05	0.36	0.30			0.16	
1.2	-0.42	-0.14	-0.12			0.40	
1.3	1.04	0.36	0.30			1.31	
1.4	0.77	0.26	0.22			0.43	
1.5	0.19	0.06	0.05			0.13	
1.6	1.07	0.37	0.30			0.42	
1.7	0.09	0.03	0.03			0.33	0.80
1.8	2.93	1.01	0.83	54.70	45.60	0.59	
1.9	1.17	0.40	0.33			0.93	
1.10	-0.04	-0.02	-0.01			0.08	
1.11	-0.30	-0.10	-0.09			0.16	
1.12	0.11	0.04	0.03			0.25	
1.13	1.60	0.55	0.46			0.08	
1.14	0.69	0.24	0.20			0.13	

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
1.15	0.30	0.10	0.09			0.08	
1.16	1.44	0.49	0.41			0.08	
1.17	-0.31	-0.10	-0.09			0.36	
1.18	0.05	0.02	0.01			0.17	
1.19	-0.34	-0.12	-0.10			0.29	
1.20	0.84	0.29	0.24			0.45	
1.21	-0.20	-0.07	-0.06			0.28	
1.22	0.14	0.05	0.04			0.06	
1.23	0.14	0.05	0.04			0.08	
1.24	1.02	0.35	0.29			0.16	
1.25	0.27	0.28	0.16			0.20	
1.26	1.06	1.09	0.62			0.31	
1.27	1.07	1.10	0.63			0.96	
1.28	2.14	2.21	1.26	3.60	ND	0.06	0.73
1.29	1.11	1.15	0.65			0.44	1.64
1.30	0.79	0.81	0.46			0.19	
1.31	1.42	1.46	0.84			0.23	1.27
1.32	1.37	1.42	0.81			0.11	1.91
1.33	0.29	0.30	0.17			0.18	
1.34	1.59	1.64	0.94	37.53	8.98	1.31	2.61
1.35	0.37	0.38	0.21			0.32	
1.36	0.70	0.72	0.41			0.17	
1.37	1.21	1.24	0.71			0.69	
1.38	0.63	0.65	0.37			0.38	
1.39	0.87	0.90	0.51			0.07	
1.40	0.71	0.73	0.42			0.26	
1.41	1.36	1.40	0.80	43.82	13.65	0.37	2.03
1.42	0.64	0.66	0.38			1.10	
1.43	0.46	0.47	0.27			0.09	
1.44	0.52	0.54	0.31			0.28	
1.45	0.74	0.76	0.44			0.15	
1.46	0.81	0.83	0.48			0.07	
1.47	0.46	0.47	0.27			0.24	
1.48	0.62	0.63	0.36			0.27	
R-690	1.70		1.00				
M-A20	0.97	1.00					
R-690	1.84		1.00				
M-A20	2.82	1.00					
1.49	0.76	0.27	0.41			0.14	
1.50	-0.22	-0.08	-0.12			0.36	
1.51	-0.35	-0.12	-0.19			0.45	
1.52	1.84	0.65	1.00	45.74	9.90	1.40	2.44
1.53	1.77	0.63	0.96	42.79	24.70	0.89	
1.54	1.08	0.38	0.59			0.80	
1.55	0.81	0.29	0.44			0.35	
1.56	1.26	0.45	0.69			0.30	
1.57	3.26	1.16	1.77	22.20	ND	1.31	2.69
1.58	0.81	0.29	0.44			0.80	
1.59	2.22	0.79	1.21	24.50	ND	1.28	2.40
1.60	0.55	0.19	0.30			0.23	
1.61	0.13	0.04	0.07			0.06	
1.62	0.75	0.27	0.41	24.89	10.25	0.25	
1.63	0.99	0.35	0.54			0.12	
1.64	3.60	1.28	1.96			0.06	0.88
1.65	0.32	0.11	0.18			0.29	
1.66	0.01	0.00	0.00			0.30	
1.67	2.00	0.71	1.09	9.30	ND	0.38	
1.68	0.86	0.30	0.47			0.21	
1.69	3.31	1.17	1.80	8.50	ND	0.22	2.39

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
1.70	3.66	1.30	1.99	24.96	12.00	0.84	2.08
1.71	2.01	0.71	1.09			0.21	
1.72	6.49	2.30	3.53	6.50	ND	0.21	1.89
1.73	19.95	0.28	0.21	3.20	ND	0.31	
1.74	19.33	0.27	0.21	5.50	ND	0.20	
1.75	22.25	0.31	0.24			0.10	
1.76	11.42	0.16	0.12			0.37	
1.77	-15.90	-0.23	-0.17			0.08	
1.78	-4.60	-0.07	-0.05			0.26	
1.79	18.78	0.27	0.20			0.25	
1.80	35.51	0.50	0.38	9.00	ND	0.71	
1.81	-4.15	-0.06	-0.04			0.33	
1.82	-37.51	-0.53	-0.40			0.17	
1.83	7.11	0.10	0.08			0.08	
1.84	-21.33	-0.30	-0.23			0.06	
1.85	-3.61	-0.05	-0.04			0.13	
1.86	-19.68	-0.28	-0.21			0.06	
1.87	-3.39	-0.05	-0.04			0.30	
1.88	55.61	0.79	0.59	5.50	ND	0.10	1.25
1.89	-6.73	-0.10	-0.07			0.17	
1.90	11.18	0.16	0.12			0.10	
1.91	-31.50	-0.45	-0.33			0.13	
1.92	-7.56	-0.11	-0.08			0.13	
1.93	-12.37	-0.18	-0.13			0.11	
1.94	49.60	0.70	0.53	14.10	ND	1.39	2.33
1.95	10.68	0.15	0.11			0.16	
1.96	144.63	2.05		63.24	74.75	0.75	0.80
R-690	94.09	1.33	1.00				
M-A20	70.64	1.00					
R-690	7.59		1.00				
M-A20	5.33	1.00					
1.97	1.47	0.28	0.19			0.37	
1.98	3.69	0.69	0.49	38.67	16.57	0.43	1.69
1.99	43.2	0.81	0.57	38.31	18.76	0.40	1.48
1.100	0.22	0.04	0.03			0.32	
1.101	2.06	0.39	0.27			0.49	
1.102	0.23	0.04	0.03			0.12	
1.103	0.33	0.06	0.04			0.28	
1.104	0.45	0.08	0.06			0.08	
1.105	4.19	0.79	0.55	37.19	12.41	0.25	2.18
1.106	4.22	0.79	0.56	46.24	30.59	1.21	1.58
1.107	0.15	0.03	0.02			0.06	
1.108	0.08	0.01	0.01			0.31	
1.109	2.70	0.51	0.36	6.5	6	0.07	
1.110	1.02	0.19	0.13			0.35	
1.111	2.55	0.48	0.34			0.10	
1.112	3.58	0.67	0.47	18.6	4.2	1.25	1.74
1.113	0.37	0.07	0.05			0.35	
1.114	-0.06	-0.01	-0.01			0.27	
1.115	0.55	0.10	0.07			0.13	
1.116	2.24	0.42	0.30			0.44	
1.117	0.56	0.10	0.07			0.27	
1.118	0.77	0.14	0.10			0.43	
1.119	0.78	0.15	0.10			0.41	
1.120	0.73	0.14	0.10			0.58	
1.121	0.21	0.05	0.03			0.40	
1.122	0.11	0.03	0.02			0.29	
1.123	0.41	0.11	0.07			0.07	
1.124	3.66	0.95	0.61	41.27	34.83	0.28	1.85

L762PHumAb	FI/CFI	FI/CFI/A20	FI/CFI/R690	FACSVRL762	FACS VR (-)	ELISA	L762/VR1013
1.125	2.67	0.69	0.44			0.27	1.55
1.126	2.36	0.61	0.39			0.86	1.71
1.127	0.70	0.18	0.12			0.11	
1.128	2.99	0.77	0.50			0.13	1.45
1.129	0.33	0.09	0.06			0.39	
1.130	0.40	0.10	0.07			0.18	
1.131	1.45	0.38	0.24			0.52	
1.132	0.33	0.08	0.05			0.25	
1.133	0.17	0.04	0.03			0.24	
1.134	0.86	0.22	0.14			0.15	
1.135	1.75	0.45	0.29			0.30	
1.136	1.35	0.35	0.23			0.07	
1.137	2.30	0.59	0.38			0.83	1.30
1.138	0.83	0.21	0.14			0.60	
1.139	1.57	0.41	0.26			0.55	
1.140	1.40	0.36	0.23			1.28	
1.142	-0.10	-0.03	-0.02			0.26	
1.143	1.46	0.38	0.24			0.16	
1.144	2.41	0.62	0.40			0.76	
R-690	6.00		1.00				
M-A20	3.86	1.00		56.4	5		
R-690	2.58	3.22	1.00				
M-A20	0.80	1.00					
1.145	0.23	0.29	0.09			0.18	
1.146	-0.12	-0.15	-0.05			0.41	
1.147	0.14	0.18	0.06			0.31	
1.148	0.09	0.11	0.03			0.43	
1.149	0.39	0.49	0.15			0.37	
1.150	2.23	2.79	0.87	17.3	5.4	0.70	1.46
1.151	0.13	0.16	0.05			0.29	
1.152	0.55	0.69	0.21			0.33	
1.154	-0.20	-0.25	-0.08			0.41	
1.155	0.16	0.19	0.06			0.23	
1.156	0.06	0.07	0.02			0.31	
1.158	0.54	0.67	0.21			0.58	
1.159	0.78	0.98	0.30			0.09	
1.160	0.23	0.29	0.09			0.08	
1.162	0.63	0.78	0.24			0.11	
1.163	0.20	0.25	0.08			0.10	
1.164	0.22	0.27	0.08			0.09	
1.166	1.41	1.76	0.55	22.9	5.3	0.52	2.41
1.167	0.32	0.40	0.12			0.08	
1.168	0.88	1.10	0.34	15.9	5.1	0.48	1.90
1.170	0.22	0.42	0.11			0.21	
1.171	0.40	0.76	0.19			0.38	
1.172	0.09	0.17	0.04			0.12	
1.174	0.23	0.43	0.11			0.15	
1.175	0.14	0.26	0.07			0.20	
R-690	2.06	3.91	1.00				
M-A20	0.53	1.00		56.4	5		
for 1.170 to 1.175							
FI-fluorescence intensity of primary antibody							
CFI-fluorescence intensity of human irrelevant primary antibody.							
A20-mouse anti-L762P monoclonal antibody							
R690-rabbit anti-L762P affinity purified polyclonal antibody							
FACS VRL762-percent positive cells from transient transfection of VR1013/L762 expression plasmid							
FACS VR(-)-percent positive cells from transient transfection of empty VR1013 expression plasmid							

EXAMPLE 32

EPITOPE MAPPING AND PURIFICATION OF hL523S-SPECIFIC ANTIBODIES

This Example describes the purification of L523S antibodies that can distinguish between human and mouse L523S homologs and will likely distinguish between hL523S and hL523S-family members such as hIMP-1 and hIMP-2.

L523S (full-length cDNA and amino acid sequence set forth in SEQ ID NO:347 and 348, respectively) is one of a family of proteins that includes hIMP-1 and hIMP-2. The members of this family of proteins have a high degree of similarity one to the other and are also highly similar between species. Thus, generating antibodies that specifically recognize human L523S (hL523S) and not other members of the protein family in humans or the mouse homologs, has been problematic. However, in order to evaluate preclinical and clinical L523S DNA/Adenoviral vaccines by detecting the protein expression of L523S, human L523S-specific antibodies are critical.

Polyclonal antibodies specific for hL523S were generated as described in Example 23. These antibodies were used to map epitopes. The epitope analysis showed 2 particular peptides of hL523S that were recognized, peptide 16/17 and peptide 32.

The amino acid sequences of both hL523S and mouse L523S (mL523S) peptide 16/17 and peptide 32 were then compared. Peptide 32/33 is identical between hL523S and mL523S. However, as the alignment below indicates, peptide 16/17 has 5 amino acid differences between the human and mouse homologs (underlined).

hL523S	(16/17)	(SEQ	ID	NO:468):
IPDEMAAQQN <u>PL</u> Q <u>Q</u> PRGRRGLGQR				
mL523S	(16/17)	(SEQ	ID	NO:469):
IPDETAAQQN <u>P</u> S <u>P</u> Q <u>L</u> RGRRGP <u>G</u> QR				

Moreover, peptide-based ELISAs showed that peptide 17 is specifically recognized by lung cancer patient sera #197, and a homology search of peptide 17 between human IMP (hIMP) family members shows that there is little similarity in this

region between family members. The hL523S peptide 17 (and 16/17) has less than 50% similarity to hL523S family members such as hIMP-1 and hIMP-2.

Based upon the epitope mapping of L523S-specific antibodies and the data from the homology search, hL523S or mL523S peptide 16/17-conjugated ligands were then used to purify human or mouse L523S-specific antibodies from rabbit polyclonal antibodies generated against hL523S protein as described in Example 23. The data from the antibodies purified by affinity chromatography using ligands conjugated with either hL523S-peptide 16/17 or mL523S-peptide 16/17 suggested that the affinity of antibodies specific to hL523S-peptide 16/17 is much higher than that of antibodies to mL523S-peptide 16/17 since they bind more strongly to hL523S-peptide 16/17 than to mL523S-peptide 16/17. The difference in affinity between the purified antibodies to human and mouse L523S-peptide 16/17 was confirmed by peptide-based ELISA. The antibodies purified by hL523S-peptide 16/17 selectively bind to human L523S-peptide 16/17 but bind much less or not at all to mL523S-peptide 16/17.

In order to further characterize the original polyclonal antibodies and antibodies purified by hL523S-peptide 16/17, immunoblot analysis was conducted using both human lung adenocarcinoma line as a source of hL523S protein and mouse whole body embryo (day 17 gestation) as the source of mL523S protein. This analysis showed that polyclonal antibodies specific for hL523S recognize hL523S protein expressed in the tumor cell line as well as mL523S protein expressed in whole body embryos of day 17 gestation. However, the addition of hL523S peptide 32/33 blocks binding of antibodies to human and mouse L523S proteins. Thus, the crossreactivity of the polyclonal antibodies to mL523S protein is due to the existence of antibodies specific to hL523S peptide 32/33. In marked contrast, the purified antibodies specific to hL523S peptide 16/17 do not bind mL523S protein expressed in mice embryos but do recognize hL523S protein expressed in human lung adenocarcinoma cells. These data confirm the ELISA data using hL523S-peptide 16/17 and mL523S-peptide 16/17 described above.

The amino acid sequence of hL523S peptide 16/17 used to purify the antibodies is about 60-70% similar to that of the mL523S-peptide 16/17 which is not recognized by hL523S-specific antibodies by Western blot analysis and peptide-based ELISA. The hL523S peptide 16/17 has less than 50% similarity to hL523S family

members such as hIMP-1 and hIMP-2. Taken together, these data suggest that it is highly probable that the antibodies purified by hL523S peptide 16/17 described herein will also distinguish hL523S protein from the other hL523S family members.

In summary, antibodies purified with the hL523S peptide 16/17 do not recognize the mouse L523S homolog. The amino acid sequence of peptide 16/17 between hL523S family members is less similar than between human and mouse L523S. Thus, the hL523S-specific antibodies described above can be used to distinguish between human and mouse L523S and between members of the hL523S family of proteins and can therefore be used for the accurate detection of hL523S protein expression in animals and humans.

EXAMPLE 33

IN VIVO IMMUNOGENECITY OF LUNG TUMOR ANTIGEN L523

This example describes two *in vivo* immunogenicity studies to evaluate the vaccination of mice with either an adenovirus containing L523 or with L523 naked DNA followed by a second immunization with an adenovirus containing L523.

The first study involved the immunization of two strains of mice with L523 adenovirus. The C57BL6 strain of mice is homozygous for HLA-type H-2^b, while strain B6D2(F1) is heterozygous for the HLA-type, H-2^{b/d}. Table 14 describes the initial immunization strategy employed.

Table 14: Immunization with L523 Adenovirus alone: Experimental Design

Group	Immunization	Strain (4/group)
1	10 ⁸ PFU Ad L523 A	C57BL6
2	10 ⁷ PFU Ad hrGFP A	C57BL6
3	10 ⁸ PFU Ad L523 A	B6D2(F1)
4	10 ⁷ PFU Ad hrGFP A	B6D2(F1)
5	Naïve	C57BL6
6	Naïve	B6D2(F1)

PFU=plaque forming unit; GFP=green fluorescent protein; Ad=adenovirus.

Mice were immunized intradermally with either 10^8 PFU of L523-adenovirus or 10^7 PFU of an irrelevant adenovirus (hrGFP). Three weeks following immunization, IgG1 and IgG2a antibody responses to L523 were examined in all groups of mice. Briefly, recombinant full length L523 (rL523) was coated onto ELISA plates and serum, at multiple dilutions, was added to the wells. Following a 60-minute incubation, the serum was washed from the wells and a secondary antibody, either specific for an IgG1 or IgG2a was added to the plates. Both antibodies were directly conjugated to horseradish peroxidase (HRP). The levels of L523 antibodies, either IgG1 or IgG2a, were measured in all groups. In the C57BL6 mice, little to no L523-specific antibodies were detected following immunization. However, in the B6D2(F1) strain of mice immunized with L523 adenovirus, both IgG1 and IgG2a L523-specific antibodies were detected at serum dilution as low as 1/1000.

In addition to detecting L523-specific antibodies in the serum, interferon-gamma (IFN- γ) responses were assayed from immune spleen cells following *in vitro* stimulation with rL523 protein. Briefly, spleen cells were harvested from all mice groups and cultured for 3 days in 96-well plates. Culture conditions included, media alone, 1 or 10 μ g/ml of rL523 protein, or 5 μ g/ml of concanavalin A (Con A). After 3 days, the supernatants were harvested and assayed for IFN- γ levels in the supernatants.

Immunization with L523-adenovirus, but not an irrelevant adenovirus, elicited a strong IFN- γ response from the spleen cells which were stimulated with rL523. In general, responses were stronger in the B6D2(F1) mouse strain, as evidenced by both a higher level of IFN- γ production, as well as the fact that stimulation with a lower antigen concentration (1 μ g/ml) elicited an equally strong response as seen with the higher antigen concentration (10 μ g/ml).

Finally, T cell proliferation responses were assayed from immune spleen cells by stimulation *in vitro* with rL523 protein. Briefly, spleen cells were cultured for 4 days in 96-well plates with, media alone, 1 or 10 μ g/ml of rL523 protein, or Con A. The cultures were then pulsed with 3H-thymidine for the final 8 hours of culture. Results are represented as the stimulation index (SI) in the presence of antigen relative to stimulation with media alone. Results were consistent with those obtained in the IFN- γ

assay. Immunization with L523-adenovirus, but not an irrelevant adenovirus, elicited a proliferation response in spleen cells stimulated with rL523. A strong SI (average of >20) was observed in spleen cells harvested from the B6D2(F1) mouse strain, with similar levels of proliferation observed at both protein concentrations. Little or no T cell proliferation was observed in the C57BL6 mouse strain.

A second study involved the immunization of two strains of mice initially with L523 naked DNA followed by a second immunization with L523 adenovirus two weeks later. The mice were harvested 3 weeks after the boost. Table 15 describes the immunization regimen of the second study.

Table 15: Immunization with L523 DNA followed by a second immunization with L523-Adenovirus: Experimental Design

Group	Immunization	Strain (4/group)
1	L523 DNA + 10^8 PFU Ad L523 A	C57BL6
2	10^8 PFU Ad L523 A	C57BL6
3	Irrelevant DNA + 10^7 PFU Ad hrGFP A	C57BL6
4	10^7 PFU Ad hrGFP A	C57BL6
5	Naïve	C57BL6
6	L523 DNA + 10^8 PFU Ad L523 A	B6D2(F1)
7	10^8 PFU Ad L523 A	B6D2(F1)
8	Irrelevant DNA + 10^7 PFU Ad hrGFP A	B6D2(F1)
9	10^7 PFU Ad hrGFP A	B6D2(F1)
10	Naïve	B6D2(F1)

PFU=plaque forming unit; GFP=green fluorescent protein; Ad=adenovirus.

As described in the first study, strong IgG1 and IgG2a antibody responses were observed in B6D2(F1) mice following immunization with L523-adenovirus. Immunizing with L523 DNA appeared to increase the overall L523-specific antibody response compared to responses achieved with immunization with L523-adenovirus alone. C57BL6 mice elicited little or no L523-specific antibody responses following immunization with L523-adenovirus, but were some slightly positive responses were detected in mice immunized with L523 DNA followed by a second immunization with L523-adenovirus.

IFN- γ responses were assayed from immune spleen cells by stimulation *in vitro* with rL523 protein. These results confirm those observed in the initial study demonstrating the immunogenicity of L523 in animals. The results also suggest that initially immunizing the animals with L523 DNA, prior to immunization with L523-adenovirus, does not significantly increase the CD4 response. As with the initial study, responses appear to be stronger in the B6D2(F1) strain of mice than the C57BL6 strain.

As with the initial study, T cell proliferation responses were assayed from immune spleen cells by stimulation *in vitro* with rL523 protein. The results from using two rounds of immunization are consistent with those obtained from the first study. Immunization with L523 DNA prior to a second round of immunization with L523-adenovirus did not significantly increase the proliferation responses generated in the mice. As with the first study, responses were stronger in the B6D2(F1) mouse strain than in the C57BL6 strain.

The difference in HLA types between the two strains of mice could explain variations in the extent of the immune responses detected. As described above, the C57BL6 strain is homozygous for H-2^b, while the B6D2(F1) is heterozygous for H-2^{b/d}. The increased diversity of the B6D2(F1) strains HLA type allows for a greater number of epitopes derived from the L523 protein to be presented. In this strain, epitopes specific for both H-2^b and H-2^d can be presented, while only H-2^b epitopes can be presented by the C57BL6 strain.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. A method for inducing an immune response in an animal, comprising:
 - a) providing a composition comprising a polynucleotide encoding at least an immunogenic portion of a lung carcinoma polynucleotide wherein the polynucleotide has at least 90% identity with SEQ ID NO:347;
 - b) administering said polynucleotide; and
 - c) thereby inducing an immune response in an animal.
2. The method of claim 1, wherein said composition further comprises a component selected from the group consisting of a physiologically acceptable carrier or an adjuvant.
3. A method according to claim 1, wherein the lung carcinoma polynucleotide is delivered by a viral based delivery system.
4. A method according to claim 3, wherein the viral based delivery system is an adenovirus.
5. The method of claim 1, wherein the immune response induced is a CD4+ T helper response.
6. The method of claim 1, wherein the immune response induced is a CD8+ cytotoxic T lymphocyte response.
7. The method of claim 1, wherein the immune response induced is both a CD4+ T helper and CD8+ cytotoxic T cell immune response.

8. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;

(b) complements of the sequences provided in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;

(c) sequences consisting of at least 10 contiguous residues of a sequence provided in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;

(d) sequences that hybridize to a sequence provided in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467, under highly stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467; and

(g) degenerate variants of a sequence provided in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467.

9. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences having at least 90% identity to a polypeptide having an amino acid sequence of any one of the sequences provided in SEQ ID NO:352, 354, 357, 361, 363, 365, 367, 369, 376-382, 387-419, 423, 427, 430, 433, 441, 443, 446, 449, 451-466 and 468-469;

(b) sequences encoded by a polynucleotide of claim 8;

(c) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 8; and

(d) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 8.

10. An expression vector comprising a polynucleotide of claim 8 operably linked to an expression control sequence.

11. A host cell transformed or transfected with an expression vector according to claim 10.

12. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 9.

13. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 9;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

14. A fusion protein comprising at least one polypeptide according to claim 9.

15. A fusion protein according to claim 14, wherein the fusion protein is selected from the group consisting of sequences provided in SEQ ID NO:352, 354, 423, 427, 430 and 433.

16. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO:351, 353, 358, 362, 364, 366, 368, 370-375, 420, 424, 428, 431, 434, 442, 447, 450 and 467 under highly stringent conditions.

17. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

- (a) polypeptides according to claim 9;
- (b) polynucleotides according to claim 8; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 8,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

18. An isolated T cell population, comprising T cells prepared according to the method of claim 17.

19. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 9;
- (b) polynucleotides according to claim 8;
- (c) antibodies according to claim 12;
- (d) fusion proteins according to claim 14;
- (e) T cell populations according to claim 18; and
- (f) antigen presenting cells that express a polypeptide according to claim 9.

20. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 19.

21. A method for the treatment of a lung cancer in a patient, comprising administering to the patient a composition of claim 19.

22. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

23. A diagnostic kit comprising at least one oligonucleotide according to claim 16.

24. A diagnostic kit comprising at least one antibody according to claim 12 and a detection reagent, wherein the detection reagent comprises a reporter group.

25. A method for the treatment of lung cancer in a patient, comprising the steps of:

- (a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 9; (ii) polynucleotides according to claim 8; and (iii) antigen presenting cells that express a polypeptide of claim 9, such that T cell proliferate;
 - (b) administering to the patient an effective amount of the proliferated T cells,
- and thereby inhibiting the development of a cancer in the patient.

SEQUENCE LISTING

<110> Corixa Corporation
Wang, Tongtong
Wang, Aijun
Skeiky, Yasir A.W.
Li, Samuel X.
Kalos, Michael D.
Henderson, Robert A.
McNeill, Patricia D.
Fanger, Neil
Retter, Marc W.
Durham, Margarita
Fanger, Gary R.
Vedvick, Thomas S.
Carter, Darrick
Watanabe, Yoshihiro
Peckman, David W.
Cai, Feng
Foy, Teresa M.

<120> COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF LUNG CANCER

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<140> PCT

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<223> n = A,T,C or G

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<222> 520, 523, 531, 540, 584, 595, 597, 609, 611, 626, 628, 651,
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ttaaaaaagg gcctgaaaaa aggggagcca caaatctgtc tgcttcctca cnttantcnt 180
tggcaaatna gcattctgtc tcnttgctg cngcctcanc ncaaaaaanc ngaactcnat 240
cnggccagg aatacatctc ncaatnaacn aaattganca aggcnnnggg aaatgccnga 300
tgggattatc ntccgcttgt tgancctcta agtttcttcc ctttcattcn accctgccag 360
ccnagttctg ttagaaaaat gccngaattc naacnccggt tttcntactc ngaatttaga 420
tctncanaaa cttcctggcc acnattcnaa ttnanggnca cgnacanatn ccttccatna 480
ancncacccc acntttgana gccangacaa tgactgcntn aantgaaggc ntgaaggaa 540
aactttgaaa ggaaaaaaa ctttgtttcc ggcccttcc aacncttctg tgttnancac 600
tgcttctcng naaccctgga agcccnngna cagtgttaca tgttgttcta nnaaacngac 660
ncttnaatnt cnatcttccc nanaacgatt ncnc 695

```

<210> 16

<211> 669

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 299, 354, 483, 555, 571, 573, 577, 642, 651, 662, 667

<223> n = A,T,C or G

<400> 16

```

cgccgaagca gcagcgcagg ttgtcccggt ttccctctcc cttcccttc tccggttgcc 60
ttcccgggcc cttactactc cacagtcccg gtcccgccat gtccagaaa caagaagaag 120
agaaccctgc ggaggagacc ggcgaggaga agcaggacac gcaggagaaa gaaggtattc 180
tgcttgagag agctgaagag gcaaagctaa aggccaaata cccaagccta ggacaaaagc 240
ctggaggctc cgacttctc atgaagagac tccagaaaagg gcaaaagtac tttgactcng 300

```

```
gagactacaa catggccaaa gccaacatga agaataagca gctgccaagt gcangaccag 360
acaagaacct ggtgactggt gatcacatcc ccaccccaca ggatctgccc agagaaagtc 420
ctcgctcgtc accagcaagc ttgcgggtgg ccaagttgaa tgatgctgcc ggggctctgc 480
canatctgag acgcttccct ccctgccccca cccgggtcct gtgctggctc ctgcccttcc 540
tgcttttgca gccangggte aggaagtggc ncnngtngtg gctggaaagc aaaacccttt 600
cctgttggtg tcccacccat ggagcccctg gggcgagccc angaacttga ncctttttgt 660
tntcttnc 669
```

<210> 17
<211> 697
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 33, 48, 50, 55, 59, 60, 76, 77, 78, 90, 113, 118, 130, 135,
141, 143, 150, 156, 166, 167, 170, 172, 180, 181, 190, 192,
194, 199, 201, 209, 212, 224, 225, 226, 230, 233, 234, 236,
242, 244, 251, 253, 256, 268, 297, 305, 308, 311, 314
<223> n = A,T,C or G

<221> misc_feature
<222> 315, 317, 322, 324, 327, 333, 337, 343, 362, 364, 367, 368,
373, 384, 388, 394, 406, 411, 413, 423, 429, 438, 449, 450,
473, 476, 479, 489, 491, 494, 499, 505, 507, 508, 522, 523,
527, 530, 533, 535, 538, 539, 545, 548, 550, 552, 555
<223> n = A,T,C or G

<221> misc_feature
<222> 562, 563, 566, 568, 572, 577, 578, 580, 581, 591, 594, 622,
628, 632, 638, 642, 644, 653, 658, 662, 663, 665, 669, 675,
680, 686, 689
<223> n = A,T,C or G

<400> 17
gcaagatatg gacaactaag tgagaaggta atnctctact gctctagntn ctccnggcnn 60
gacgcgctga ggagannnac gctggcccan ctgccggcca cacacgggga tcntggtnat 120
gcctgcccان ggانcccca ncnctcgان ccatntcac accganncn tncgcccان 180
ncctggctcn cncngcccng nccagctcnc gnccccctcc gccnnnctcn ttncntctc 240
cncnccctcc ncnacnacct cctaccncg gctccctccc cagccccccc ccgcaancct 300
ccacnacncc ntcnnncga ancnccnctc genctengcc cngccccct gcccccgcc 360
cncnacnncg cgncccccg cgcncgcngc ctncccccct cccacnacag ncnacccgc 420
agnacgcnc tcgcccنct gacgcccنn cccgcgcgc tcacctcat ggnccnacng 480
ccccgctcnc ncnctgcnc gccgnncng cgcgccgcc cnnccngtn cncncgng 540
ccccngcngn angcngtgc cncangncc gngccgnncn ncacctccg ncnccgcc 600
cgcccgctgg gggctcccgc cncgcggntc antcccncc cntncgcca cntccgntc 660
cnnnctcnc gctcngcgn cgcncncnc ccccc 697

<210> 18
<211> 670
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 234, 292, 329, 437, 458, 478, 487, 524, 542, 549, 550, 557,
576, 597, 603, 604, 646, 665
<223> n = A,T,C or G

<400> 18

```
ctcgtgtgaa ggggtgcagta cctaagccgg agcggggtag aggcggggccg gcacccccctt 60
ctgacctcca gtgccgcggg cctcaagatc agacatggcc cagaacttga acgacttggc 120
gggacggctg cccgcgcggg cccggggcat gggcacggcc ctgaagctgt tgctgggggc 180
cggcgccgtg gccacgggtg tgccggaatc tgtgttcacc gtggaaggcg ggcncagagc 240
catcttcttc aatcggatcg gtggagtgc caggacacta tcctggggcg anggccttca 300
cttcaggatc cttgggtcca gtacccanc atctatgaca ttccggccag acctcgaaaa 360
aatctcctcc ctacaggctc caaagaccta cagatggtga atatctccct gcgagtgttg 420
tctcgaccaa tgctcangaa cttcctaaca tgttccancg cctaagggtt ggactacnaa 480
gaacgantgt tgccgtccat tgtcacgaag tgctcaagaa ttinggtggc caagttcaat 540
gncctcacnn ctgatcnccc agcggggcca agttanccct ggttgatccc cgggganctg 600
acnnaaaagg gccaaaggact tcccctcatc ctggataatg tggcctcac aaagctcaac 660
tttanccacc 670
```

<210> 19

<211> 606

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 506

<223> n = A,T,C or G

<400> 19

```
actagtgcc aactcagctc ccaggccagt tctctgaatg tcgaggagtt ccaggatctc 60
tggtcctcagt tgctccttggg tattgatggg ggacaaattg gggatggcca gagccccgag 120
tgtgccttg gctcaactgt gggtgatttg tctgtgcccg gaaagtgttg catcattcgt 180
ccaggctgtg ccctggaaag tactacagcc atcctccaac agaagtacgg actgctcccc 240
tcacatgcgt cctacctgtg aaactctggg aagcaggaag gccaagacc tgggtctgga 300
tactatgtgt ctgtccactg acgactgtca aggcctcatt tgcagaggcc accggagcta 360
gggcactagc ctgactttta aggcagtgtg tctttctgag cactgtagac caagcccttg 420
gagctgctgg tttagccttg cacttgggga aaggatgtat ttatttgtat ttcatatat 480
cagccaaaag ctgaatggaa aagttanagaa cattcctagg tggccttatt ctaataagtt 540
tcttctgtct gttttgtttt tcaattgaaa agttattaaa taacagattt agaattctagt 600
gagacc 606
```

<210> 20

<211> 449

<212> DNA

<213> Homo sapiens

<400> 20

```
actagtaaac aacagcagca gaaacatcag tatcagcagc gtcgccagca ggagaatatg 60
cagcgccaga gccgaggaga acccccgtc cctgaggagg acctgtccaa actcttcaaa 120
ccaccacagc cgcttgccag gatggactcg ctgctcattg caggccagat aaacacttac 180
tgccagaaca tcaaggagtt cactgcccaa aacttaggca agctcttcat ggcccaggct 240
cttcaagaat acaacaacta agaaaaggaa gtttccagaa aagaagttaa catgaactct 300
tgaagtcaca ccagggaac tcttgaaga aatatatttg catattgaaa agcacagagg 360
atttcttttag tgctattgcc gattttggct ataacagtgt ctttctagcc ataataaaat 420
aaaacaaaat cttgactgct tgctcaaaa 449
```

<210> 21

<211> 409

<212> DNA

<213> Homo sapiens

```

<400> 21
tatcaatcaa ctggtgaata attaaacaat gtgtggtgtg atcatacaaa ggggtaccact 60
caatgataaa aggaacaagc tgcctatatg tggacaaca tggatgcatt tcagaaactt 120
tatgttgagt gaaagaacaa acacggagaa cactactatgt ggttctcttt atgtaacatt 180
acagaaataa aaacagaggc aaccaccttt gaggcagtat ggagtgaat agactggaaa 240
aaggaaggaa ggaactcta cgctgatgga aatgtctgtg tcttcattgg gtggtagtta 300
tgtggggata tacatttgtc aaaatttatt gaactatata ctaaagaact ctgcatttta 360
ttgggatgta aataatacct caattaaaaa gacaaaaaaa aaaaaaaaaa 409

```

```

<210> 22
<211> 649
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 263, 353, 610, 635, 646
<223> n = A,T,C or G

```

```

<400> 22
acaattttca ttatcttaag cacattgtac atttctacag aacctgtgat tattctcgca 60
tgataaggat ggtacttgca tatggtgaat tactactgtt gacagtttcc gcagaaatcc 120
tatttcagtg gaccaacatt gtgcatggc agcaaatgcc aacattttgt ggaatagcag 180
caaactaca agagaccctg gttggttttt cgttttgttt tctttgtttt ttcccccttc 240
tctgaaatca gcagggatgg aangagggtta gggaagtat gaattactcc ttccagtagt 300
agctctgaag tgtcacattt aatatcagtt ttttttaaac atgattctag ttnaatgtag 360
aagagagaag aaagaggaag tgttcacttt ttttaatacac tgatttagaa atttgatgtc 420
ttatatcagt agttctgagg tattgatagc ttgctttatt tctgccttta cgttgacagt 480
gttgaagcag ggtgaataac taggggcata tatatttttt ttttttgtaa gctgtttcat 540
gatgttttct ttggaatttc cggataagtt caggaaaaa cctgcagtgt gttatctagt 600
ctgaagttcn tatccatctc attacaacaa aaacncccag aacggnnttg 649

```

```

<210> 23
<211> 669
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 642, 661
<223> n = A,T,C or G

```

```

<400> 23
actagtgcg tactggctga aatccctgca ggaccaggaa gagaaccagt tcagactttg 60
tactctcagt caccagctct ggaattagat aaattccttg aagatgtcag gaatgggatc 120
tactctctga cagccttttg gctgcctcgg ccccgacagc cacagcagga ggaggtgaca 180
tcacctgtcg tgccccctc tgtcaagact cgcacacctg aaccagctga ggtggagact 240
cgcaagggtg tgcctgatga gtgcaacatt gagtcggttg agggaggagt caaacaccac 300
ctgacacttc tgcctgaagt ggaggacaaa ctgaaccggc acctgagctg tgacctgatg 360
ccaaatgaga atatccccga gttggcggct gagctgggtc agctgggctt cattagttag 420
gctgaccaga gccggttgac ttctctgcta gaagagactt gaacaagtto aattttgcca 480
ggaacagtac cctcaactca gccgctgtca ccgtctcctc ttagagctca ctggggccag 540
gccctgatct gcgctgtggc tgcctggac gtgctgcacc ctctgtcctt cccccagtc 600
agtattacct gtgaagccct tccctccttt attattcagg anggctgggg gggctccttg 660
nttctaacc
669

```

```

<210> 24
<211> 442

```

<212> DNA

<213> Homo sapiens

<400> 24

```
actagtacca tcttgacaga ggatacatgc tcccaaaaacg tttgttacca cacttaaaaa 60
tcaactgccat cattaagcat cagtttcaaaa attatagcca ttcattgattt actttttcca 120
gatgactatc attattctag tcccttgaat ttgtaagggg aaaaaaaaca aaaacaaaaa 180
cttacgatgc acttttctcc agcacatcag atttcaaatt gaaaattaaa gacatgctat 240
ggtaatgcac ttgctagtac tacacacttt ggtacaacaa aaaacagagg caagaaacaa 300
cggaaagaga aaagcccttc tttgttgccc cttaaactga gtcaagatct gaaatgtaga 360
gatgatctct gacgatacct gtatgttctt attgtgtaaa taaaattgct ggtatgaaat 420
gacctaaaaa aaaaaaaaga aa                                     442
```

<210> 25

<211> 656

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 330, 342, 418, 548, 579, 608

<223> n = A,T,C or G

<400> 25

```
tgaagtgacc acacactggt tgaattttgc acaaaaagtg actgtaggat caggtgatag 60
ccccggaatg tacagtgtct tgggtcacca agatgccttc taaaggctga cataccttgg 120
accctaattg ggcagagagt atagccctag cccagtgggtg acatgaccac tccctttggg 180
aggcctgagg tagaggggag tggatatgtt tttctcagtg gaagcagcac atgagtgggt 240
gacaggatgt tagataaagg ctctagttag ggtgtcattg tcatttgaga gactgacaca 300
ctcctagcag ctggttaaagg ggtgctggan gccatggagg anctctagaa acattagcat 360
gggctgatct gattacttcc tggcatcccg ctacacttta tgggaagtct tattagangg 420
atgggacagt tttccatata cttgctgtgg agctctggaa cactctctaa atttccctct 480
attaaaaatc actgccctaa ctacacttcc tccctgaagg aatagaaatg gaactttctc 540
tgacatantt ctgtgcatgg ggagccagcc acaaatgana atctgaacgt gtccagggtt 600
ctcctganac tcactacat agaattggtt aaacctccc ttggaataag gaaaaa 656
```

<210> 26

<211> 434

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 395

<223> n = A,T,C or G

<400> 26

```
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctagggtgtt ccatctatgt ttcaatctgt ccatctacca ggcctcgcca taaaaacaaa 120
acaaaaaac gctgccaggt tttagaagca gttctggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaggga atttggcttt cacttcatct 240
aataactgaa ttgtcaggct ttgattgata attgtagaaa taagtacgct tctgttgttg 300
gaataagtta taatcagtat tcactctctt gttttttgtc actcttttct ctctaattgt 360
gtcattttgt ctgtttgaaa aatatttctt ctatnaaatt aaactaacct gccttaaaaa 420
aaaaaaaaaa aaaa                                     434
```

<210> 27

<211> 654

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 505, 533, 563, 592, 613, 635, 638

<223> n = A,T,C or G

<400> 27

```
actagtccaa cacagtcaga aacattgttt tgaatcctct gtaaaccaag gcattaatct 60
taataaacca ggatccattt aggtaccact tgatataaaa aggatatcca taatgaatat 120
tttatactgc atcctttaca ttagccacta aatacgttat tgcttgatga agacctttca 180
cagaatccta tggattgcag catttcactt ggctacttca taccatgcc ttaaagaggg 240
gcagtttctc aaaagcagaa acatgccgcc agttctcaag ttttcctcct aactccattt 300
gaatgtaagg gcagctggcc cccaatgtgg ggaggtccga acattttctg aattcccatt 360
ttcttgttcg cggtctaaatg acagtttctg tcattactta gattccgata tttcccaaag 420
gtgttgattt acaaagaggc cagctaatac cagaaatcat gaccctgaaa gagagatgaa 480
attcaagctg tgagccaggc agganctcag tatggcaaaag gtcttgagaa tcngccattt 540
ggtacaaaaa aaatttttaa gcnthttatgt tataccatgg aacctagaa anggcaaggg 600
aattgttaag aanaatttta agtgtccaga ccanaaanga aaaaaaaaaa aaaa 654
```

<210> 28

<211> 670

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 101, 226, 274, 330, 385, 392, 397, 402, 452, 473, 476, 532, 534, 538, 550, 583, 595, 604, 613, 622, 643, 669

<223> n = A,T,C or G

<400> 28

```
cgtgtgcaca tactgggagg atttccacag ctgcacggtc acagccctta cggattgcc 60
ggaaggggcg aaagatatgt gggataaact gagaaaagaa nccaaaaacc tcaacatcca 120
aggcagctta ttcgaaactct gcggcagcgg caacggggcg gcgggggtccc tgcctccggc 180
gttcccgggtg ctctctgtgt ctctctcggc agcttttagcg acctgncctt ccttctgagc 240
gtggggccag ctccccccgc ggcgccacc cactctcact ccatgctccc ggaaatcgag 300
aggaagatca ttagtctttt ggggacgttn gtgattctct gtgatgctga aaaacactca 360
tatagggaat gtgggaaatc ctganctctt tnttatntcg tntgatttct tgtgttttat 420
ttgccaaaat gttaccaatc agtgaccaac cnagcacagc caaaaatcgg acntcngctt 480
tagtccgtct tcacacacag aataagaaaa cggcaaaccc accccacttt tnanthttat 540
tattactaan ttttttctgt tgggcaaaag aatctcagga acngccctgg ggccnccgta 600
ctanagttaa ccnagctagt tncatgaaaa atgatgggct ccnctcaat gggaaagcca 660
agaaaaagnc
```

<210> 29

<211> 551

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 336, 474, 504, 511, 522, 523, 524, 540, 547

<223> n = A,T,C or G

<400> 29

```
actagtcctc cacagcctgt gaatccccct agacctttca agcatagtga gcggagaaga 60
```

```

agatctcagc gtttagccac cttacccatg cctgatgatt ctgtagaaaa ggtttcttct 120
ccctctccag ccactgatgg gaaagtattc tccatcagtt ctcaaaatca gcaagaatct 180
tcagtaccag aggtgcctga tgttgacatc ttgccacttg agaagctggg accctgtctc 240
cctcttgact taagtcgtgg ttcagaagtt acagcaccgg tagcctcaga ttcctcttac 300
cgtaaatgaat gtcccagggc agaaaaagag gatacncaga tgcttccaaa tccttcttcc 360
aaagcaatag ctgatgggaa gaggagctcc agcagcagca ggaatatoga aaacagaaaa 420
aaaagtgaat ttgggaagac aaaagctcaa cagcatttgg taaggagaaa aganaagatg 480
aggaaggaag agagaagaga gacnaagatc nctacggacc gnnncgggag aagaagaagn 540
aaaaaanaaa a 551

```

```

<210> 30
<211> 684
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 545, 570, 606, 657, 684
<223> n = A,T,C or G

```

```

<400> 30
actagtctta tctggaaaaa gcccggttg gaagaagctg tggagagtgc gtgtgcaatg 60
cgagactcat ttcttggaaag catccctggc aaaaatgcag ctgagtacaa ggttatcact 120
gtgatagaac ctggactgct ttttgagata atagagatgc tgcagtctga agagacttcc 180
agcacctctc agttgaatga attaatgatg gcttctgagt caactttact ggctcaggaa 240
ccacgagaga tgactgcaga tgtaatcgag cttaaaggga aattcctcat caacttagaa 300
ggtggtgata ttcgtgaaga gtcttcttat aaagtaattg tcatgccgac tacgaaagaa 360
aaatgcccc gttgttggaa gtatacagcg ggagtcttca gatacactgt gtcctcgatg 420
tgcagaagtt gtcagtggga aaatagtatt aacagctcac tgcagcaaga accctcctga 480
cagtactggg ctagaagttt ggatggatta tttacaatat aggaaagaaa gccaagaatt 540
aggtnatgat tggatgagta aatgggtggan gatggggaat tcaaatcaga attatggaag 600
aagtntttcc tgttactata gaaaggaatt atgtttattt acatgcagaa aatatanatg 660
tgtggtgtgt accgtggatg gaan 684

```

```

<210> 31
<211> 654
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 326, 582, 651
<223> n = A,T,C or G

```

```

<400> 31
gcgcagaaaa ggaaccaata tttcagaaac aagcttaata ggaacagctg cctgtacatc 60
aacatcttct cagaatgacc cagaagttat catcgtggga gctggcgtgc ttggctctgc 120
tttggcagct gtgctttcca gagatggaag aaaggtgaca gtcattgaga gagacttaaa 180
agagcctgac agaatagttg gagaattcct gcagccgggt gggttatcatg ttctcaaaga 240
ccttggctct ggagatacag tggaaggtct tgatgccag gttgtaaatg gttacatgat 300
tcatgatcag ggaagcaaaa tcagangttc agattcctta ccctctgtca gaaaacaatc 360
aagtgcagag tggaagagct ttocatcacg gaagattcat catgagtctc cggaagcag 420
ctatggcaga gcccaatgca aagtttattg aaggtgttgt gttacagtta ttagaggaag 480
atgatgttgt gatgggagtt cagtacaagg ataaagagac tgggagatat caaggaactc 540
catgctccac tgactgttgt tgcagatggg cttttctcca anttcaggaa aagcctggtc 600
tcaataaagt ttctgtatca ctcatattgg tggcttctta tgaagaatgc nccc 654

```

```

<210> 32

```


<211> 673
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 376, 545, 627
<223> n = A,T,C or G

<400> 32
actagtgaag aaaaagaaat tctgatacgg gacaaaaatg ctcttcaaaa catcattctt 60
tatcacctga caccaggagt ttctattgga aaaggatttg aacctggtgt tactaacatt 120
ttaagacca cacaaggaag caaaatcttt ctgaaagaag taaatgatac acttctggtg 180
aatgaattga aatcaaaaaga atctgacatc atgacaacaa atggtgtaat tcatgttgta 240
gataaactcc tctatccagc agacacacct gttggaatg atcaactgct gaaataactt 300
aataaattaa tcaaatatcat ccaaattaag tttgttcgtg gtagcacctt caaagaaatc 360
cccgtagctg tctatnagcc aattattaaa aaatacacca aaatcattga tgggagtgcc 420
tgtgggaaat aactgaaaaa gagaccgaga agaacgaatc attacaggtc ctgaaataaa 480
atacctagga tttctactgg aggtggagaa acagaagaac tctgaagaaa ttgttacaag 540
aagangtccc aaggtcacca aattcattga aggtggtgat ggtctttatt tgaagatgaa 600
gaaattaaaa gacgcttcag ggagacnccc catgaaggaa ttgccagcca caaaaaaatt 660
cagggattag aaa 673

<210> 33
<211> 673
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 325, 419, 452, 532, 538, 542, 571, 600, 616, 651, 653, 672
<223> n = A,T,C or G

<400> 33
actagttatt tactttcttc cgcttcagaa ggtttttcag actgagagcc taagcatact 60
ggatctgttg tttcttttgg gtctcacctc atcagtgtgc atagtggcag aaattataaa 120
gaaggttgaa aggagcaggg aaaagatcca gaagcatgtt agttcgacat catcatcttt 180
tcttgaagta tgatgcataat tgcattatct tatttgcaaa ctaggaattg cagtctgagg 240
atcatttaga agggcaagtt caagaggata tgaagatttg agaacttttt aactattcat 300
tgactaaaaa tgaacattaa tgttnaagac ttaagacttt aacctgctgg cagtcccaaa 360
tgaaattatg caactttgat atcatattcc ttgattttaa ttgggctttt gtgattgant 420
gaaactttat aaagcatatg gtcagttatt tnattaaaaa ggcaaaacct gaaccacctt 480
ctgcacttaa agaagtctaa cagtacaaat acctatctat cttagatgga tntatttntt 540
tntattttta aatattgtac tatttatggt nggtggggct ttcttactaa tacacaaatn 600
aatttatcat ttcaanggca ttctatttgg gtttagaagt tgattccaag nantgcata 660
ttcgctactg tnt 673

<210> 34
<211> 684
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 414, 472, 480, 490, 503, 507, 508, 513, 523, 574, 575, 598,
659, 662, 675
<223> n = A,T,C or G

```

<400> 34
actagtttat tcaagaaaag aacttactga ttctctgtgt cctaaagcaa gagtggcagg 60
tgatcagggc tgggtgtagca tccggttctt ttagtgagc taactgcatt tgtcactgat 120
gaccaaggag gaaatcacta agacatttga gaagcagtgg tatgaacgtt cttggacaag 180
ccacagttct gagccttaac cctgtagttt gcacacaaga acgagctcca cctcccttc 240
ttcaggagga atctgtgctg atagattggc tggacttttc aatgggtctg ggttgcaagt 300
gggactgtt atggctgggt atggagcgga cagccccagg aatcagagcc tcagcccgcc 360
tgcttggtg gaaggtacag gtgttcagca ccttcggaaa aagggcataa agtngtggg 420
gacaattctc agtccaagaa gaatgcattg accattgctg gctatttgct tncctagtan 480
gaattggatn catctttgac cangatnntt ctncatgct ttnttgcaat gaaatcaa 540
cccgatttat ctacaagtgg tatgaagtc tgcnncccc agagaggctg ttcaggcnat 600
gtcttccaag ggcagggtgg gttacaccat ttacctccc ctctccccc agattatgna 660
cncagaagga attntttcc tccc 684

```

```

<210> 35
<211> 614
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 17, 20, 152, 223, 267, 287, 304, 306, 316, 319, 321, 355,
365, 382, 391, 407, 419, 428, 434, 464, 467, 477, 480, 495,
499, 505, 515, 516, 522, 524, 527, 542, 547, 549, 567, 572,
576, 578
<223> n = A,T,C or G

```

```

<400> 35
actagtccaa cgcgttngcn aatattcccc tggtagccta ctcccttacc cccgaatatt 60
ggtaagatcg agcaatggct tcaggacatg gggtctcttc tctgtgatc attcaagtgc 120
tactgcatg aagactggct tgtctcagtg tntcaacctc accagggtg tctcttggtc 180
cacacctgc tccctgttag tgccgtatga cagcccccac canatgacct tggccaagtc 240
acggtttctc tgtggtcaat gttggtnggc tgattggtgg aaagtanggt ggaccaaagg 300
aagncncgtg agcagncanc nccagttctg caccagcagc gcctccgtcc tactnggggtg 360
ttcngtttc tcttgcccct gngtgggcta nggcctgatt cgggaanatg cctttgcang 420
gaaggganga taantgggat ctaccaattg attctggcaa aacnatntct aagattnttn 480
tgctttatgt ggganacana tctanctctc atttnntgct gnanatnaca ccctactcgt 540
gntcgancnc gtcttcgatt ttcgganaca cncantnaa tactggcggt ctgttggtta 600
aaaaaaaaaa aaaa 614

```

```

<210> 36
<211> 686
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 222, 224, 237, 264, 285, 548, 551, 628, 643, 645, 665, 674
<223> n = A,T,C or G

```

```

<400> 36
gtggctggcc cggttctccg cttctcccca tcccctactt tctccctcc ctccctttcc 60
ctccctcgtc gactgttgct tgetggctgc agactccctg acccctccct caccctcccc 120
taacctcggt gccaccgat tgcccttctt ttctgttgcc ccagcccagc cctagtgtca 180
gggcgggggc ctggagcagc ccgaggcact gcagcagaag ananaaaaga cacgacnaac 240
ctcagctcgc cagtccggtc gctngcttcc cgccgcatgg caatnagaca gacgccgctc 300
acctgctctg ggcacacgcg acccggtggtt gatttggcct tcagtggcat cacccttatg 360
ggtatttctt aatcagcgct tgcaaagatg gttaacctat gctacgccag ggagatacag 420

```

```

gagactggat tggaacattt ttgggggtcta aagggtctgtt tgggggtgcaa cactgaataa 480
ggatgccacc aaagcagcta cagcagctgc agatttcaca gcccaagtgt gggatgctgt 540
ctcagganatt naattgataa cctggctcat aacacattgt caagaatgtg gatttcccca 600
ggatattatt atttgtttac cggggganag gataactgtt tcncntattt taattgaaca 660
aactnaaaca aaanctaagg aaatcc 686

```

```

<210> 37
<211> 681
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 7, 10, 11, 19, 25, 32, 46, 53, 77, 93, 101, 103, 109, 115,
123, 128, 139, 157, 175, 180, 192, 193, 194, 212, 218, 226,
227, 233, 240, 241, 259, 260, 267, 289, 296, 297, 298, 312,
313, 314, 320, 325, 330, 337, 345, 346, 352, 353, 356
<223> n = A,T,C or G

```

```

<221> misc_feature
<222> 382, 385, 400, 427, 481, 484, 485, 491, 505, 515, 533, 542,
544, 554, 557, 560, 561, 564, 575, 583, 589, 595, 607, 619,
628, 634, 641, 645, 658, 670
<223> n = A,T,C or G

```

```

<400> 37
gagacanaacn naacgtcang agaanaaaag angcatggaa cacaanccag gcncgatggc 60
caccttccca ccagcancca gcgcccccca gcngccccca ngncgggang accangactc 120
cancctgnat caatctganc tctattcctg gcccatnccct acctcggagg tggangccgn 180
aaaggtcgca cnnncagaga agctgctgcc ancaccancc gccccnnccc tgnccgggctn 240
nataggaaac tggtagaccnn gctgcanaat tcatacagga gcacgcgang ggcacnnnct 300
cacactgagt tnnngatgan gcctnaccan ggacctnccc cagcnnattg annacnggac 360
tgccggaggaa ggaagacccc gnacnggatc ctggcccgcn tgccaccccc ccaccocctag 420
gattatnccc cttgactgag tctctgaggg gctaccogaa cccgcctcca ttccctacca 480
natnntgctc natcgggact gacangctgg ggatnggagg ggctatcccc cancatcccc 540
tnanaccaac agcnacngan natnggggct ccccnngggtc ggngcaacnc tcctncccc 600
cggcgcnngc cttcgggtgt gtcctccntc aacnaattcc naaanggcgg gccccccngt 660
ggactcctcn ttgttcctc c 681

```

```

<210> 38
<211> 687
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 3, 30, 132, 151, 203, 226, 228, 233, 252, 264, 279, 306,
308, 320, 340, 347, 380, 407, 429, 437, 440, 445, 448, 491,
559, 567, 586, 589, 593, 596, 603, 605, 606, 609, 626, 639,
655, 674, 682
<223> n = A,T,C or G

```

```

<400> 38
canaaaaaaa aaaacatggc cgaaccagn aagctgcgcg atggcgccac ggccccctctt 60
ctccccgctt gtgtccggaa ggttccctc cgaggcgccc cggtccccgc aagcggagga 120
gagggcgagg cntgccgggg ccggagctca nagggcctgg ggccgctctg ctctccccgc 180
atcgcaaggg cggcgctaac ctnaggcctc cccgcaaagg tccccnangc ggngggcgcg 240
gggggctgtg anaaccgcaa aaanaacgct gggcgcgcn cgaaccgctc ccccccgcg 300

```

```

aaggananac ttccacagan gcagcggttc cacagcccan agccacnttt ctagggtgat 360
gcacccagtg aagtctcctgn cggggaagct caccgctgtc aaaaaanctc ttcgctccac 420
cggcgacacna agggggangan ggcangangc tgccgcccgc acagggtcatc tgatcacgtc 480
gcccccccta ntctgctttt gtgaatctcc actttgttca accccaccgc ccgttctctc 540
ctccttgccg cttcctctna ccttaanaac cagcttcctc taccnctatg tanttctctc 600
gcncnngtng aaattaattc ggccnccgg aacctcttnc ctgtggcaac tgctnaaaga 660
aactgctggt ctgnttactg cngtccc 687

```

<210> 39

<211> 695

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 300, 401, 423, 429, 431, 437, 443, 448, 454, 466, 492, 515,
523, 524, 536, 538, 541, 552, 561, 566, 581, 583, 619, 635,
636, 641, 649, 661, 694

<223> n = A,T,C or G

<400> 39

```

actagtctgg cctacaatag tgtgattcat gtaggacttc tttcatcaat tcaaaacccc 60
tagaaaaacg tatacagatt atataagtag ggataagatt tctaacattt ctgggctctc 120
tgacccctgc gctagactgt ggaaagggag tattattata gtatacaaca ctgctgttgc 180
cttattagtt ataacatgat aggtgctgaa ttgtgattca caatttaaaa acaactgtaat 240
ccaaactttt ttttttaact gtagatcatg catgtgaatg ttaatgttaa ttgtttcaan 300
gttggttatg gtgaaaaaaa ccacatgcct taaaatttta aaaagcaggg cccaaactta 360
ttagtttaaa attaggggta tgtttccagt ttgttattaa ntgggttatg ctctgtttag 420
aanaaatcna ngaacangat ttngaaantt aagntgacat tatttnccag tgacttggtta 480
atttgaatc anacacggca ccttccggtt tggtnctatt ggnntttgaa tccaancngg 540
ntccaaatct tnttggaaac ngtcnntta acttttttac nanatcttat ttttttattt 600
tggaatggcc ctatttaang ttaaaagggg ggggnnccac naccattcnt gaataaaact 660
naatatatat ccttgggtccc ccaaattta agng 695

```

<210> 40

<211> 674

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 403, 428, 432, 507, 530, 543, 580, 583, 591, 604, 608, 621,
624, 626, 639, 672

<223> n = A,T,C or G

<400> 40

```

actagtagtc agttgggagt ggttgctata ccttgacttc atttatatga atttccactt 60
tattaaataa tagaaaagaa aatcccgggtg cttgcagtag agttatagga cattctatgc 120
ttacagaaaa tatagccatg attgaaatca aatagtaaag gctgttctgg ctttttatct 180
tcttagctca tcttaataaa gtagtacact tgggatgcag tgcgtctgaa gtgctaatac 240
gttgtaacaa tagcacaaat cgaacttagg atgtgtttct tctcttctgt gtttcgattt 300
tgatcaattc tttaattttg ggaacctata atacagtttt cctattcttg gagataaaaa 360
ttaaatggat cactgatatt taagtcattc tgcttctcat ctnaatattc catattctgt 420
attagganaa antacctccc agcacagccc cctctcaaac cccacccaaa accaagcatt 480
tggaatgagt ctccttttatt tccgaantgt gggatgtata acccatatcn ctccaatttc 540
tgnttgggtt ggggtattaat ttgaactgtg catgaaaagn ggnaatcttt nctttgggtc 600
aaantttnc ggtaatttg nctngncaaa tccaatttnc ttttaaggggtg tctttataaa 660
atttgctatt cngg 674

```

<210> 41
<211> 657
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 243, 247, 251, 261, 267, 272, 298, 312, 315, 421, 432, 434,
501, 524, 569, 594, 607, 650
<223> n = A,T,C or G

<400> 41
gaaacatgca agtaccacac actgtttgaa ttttgcacaa aaagtgactg tagggatcag 60
gtgatagccc cggaatgtac agtgtcttgg tgcaccaaga tgccttctaa aggctgacat 120
accttgggac cctaattggg cagagagtat agccctagcc cagtgggtgac atgaccactc 180
cctttgggag gctgaagtta aagggaatgg tatgtgtttt ctcatggaag cagcacatga 240
atnggtnaca ngatgttaaa ntaaggntct antttgggtg tcttgtcatt tgaaaaantg 300
acacactcct ancantcgtt aaaggggtgc tggaagccat ggaagaactc taaaaacatt 360
agcatgggct gatctgatta ctctctggca tcccgctcac ttttatggga agtcttatta 420
naaggatggg ananttttcc atatccttgc tgttggaact ctggaacact ctctaaattt 480
ccctctatta aaaatcactg nccttactac acttctcctc tganggaata gaaatggacc 540
tttctctgac ttagttcttg gcatggganc cagcccaaat taaaatctga cttntccggt 600
ttctcncgaa ctcacctact tgaattggta aaacctcctt tgggaattagn aaaaacc 657

<210> 42
<211> 389
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 179, 317, 320
<223> n = A,T,C or G

<400> 42
actagtgtcg aggaatgtaa acaagtttgc tgggccttgc gagacttcac cagggtgttt 60
cgatagctca cactcctgca ctgtgcctgt caccaggaa tgcctttttt aattagaaga 120
caggaagaaa acaaaaacca gactgtgtcc cacaatcaga aacctccgtt gtggcagang 180
ggccttcacc gccaccaggg tgtcccgcc aacagggaga gactccagcc ttctgaggcc 240
atcctgaaga attcctgttt gggggttgtg aaggaaaatc acccggtatt aaaaagatgc 300
tggtgcctgc ccgcgtngtn gggaaggagc tggtttcctg gtgaatttct taaaagaaaa 360
atattttaag ttaagaaaaa aaaaaaaaaa 389

<210> 43
<211> 279
<212> DNA
<213> Homo sapiens

<400> 43
actagtgaca agctcctggt cttgagatgt cttctcgtta aggagatggg ccttttggag 60
gtaaaggata aaatgaatga gttctgtcat gattcactat tctagaactt gcatgacatt 120
tactgtgtta gctctttgaa tgttcttgaa attttagact ttctttgtaa acaataata 180
tgtccttatac attgtataaa agctgttatg tgcaacagtg tggagatcct tgtctgattt 240
aataaaatc ttaaacactg aaaaaaaaaa aaaaaaaaaa 279

<210> 44
<211> 449

<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 245, 256, 264, 266, 273, 281, 323, 325, 337, 393
<223> n = A,T,C or G

<400> 44
actagtagca tctttttctac aacgttaaaa ttgcagaagt agcttatcat taaaaaaca 60
caacaacaac aataacaata aatcctaagt gtaaatcagt tattctaccc cctaccaagg 120
atatcagcct gttttttccc tttttttctcc tgggaataat tgtgggcttc ttcccaaatt 180
tctacagcct ctttcctctt ctcatgcttg agcttccttg tttgcaogca tgcgttgtgc 240
aagantgggc tgtttngctt ggantncggt ccnagtggaa ncatgctttc ccttggtact 300
gttgaagaa actcaaacct tcnancccta ggtgttncca ttttgtcaag tcatcactgt 360
atttttgtac tggcattaac aaaaaaagaa atnaaatatt gttccattaa actttaataa 420
aactttaaaa gggaaaaaaa aaaaaaaaaa 449

<210> 45
<211> 559
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 263
<223> n = A,T,C or G

<400> 45
actagtgtgg ggggaatcacg gacacttaaa gtcaatctgc gaaataattc ttttattaca 60
cactcactga agtttttgag tcccagagag ccattctatg tcaaacattc caagtactct 120
ttgagagccc agcattacat caacatgccg gtgcagttca aaccgaagtc cgcaggcaaa 180
tttgaagctt tgcttgctat tcaaacagat gaaggcaaga gtattgctat tgcactaatt 240
ggtgaagctc ttggaaaaaa ttactagaaa tactttttgt gtttaagttaa ttacataagt 300
tgtattttgt taactttatc tttctacact acaattatgc ttttgtatat atattttgta 360
tgatggatat ctataattgt agattttggt tttaacaagct aatactgaag actcgactga 420
aatattatgt atctagccca tagtattgta cttaactttt acagggtgaa aaaaaaattc 480
tgtgtttgca ttgattatga tattctgaat aaatatggga atatatttta atgtgggtaa 540
aaaaaaaaaa aaaaaggaa 559

<210> 46
<211> 731
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 270, 467, 477, 502, 635, 660, 671, 688, 695, 697, 725
<223> n = A,T,C or G

<400> 46
actagttcta gtaccatggc tgtcatagat gcaaccatta tattccattt agtttcttcc 60
tcagggtccc taacaattgt ttgaaactga atatatatgt ttatgtatgt gtgtgtgttc 120
actgtcatgt atatgggtga tatgggatgt gtgcagtttt cagttatata tatattcata 180
tatacatatg catatatatg tataatatac atatatacat gcatacactt gtataatata 240
catatatata cacatatatg cacacatatn atcactgagt tccaaagtga gtcttttatt 300
ggggcaattg tattctotcc ctctgtctgc tcaactggcc tttgcaagac atagcaattg 360
cttgatttcc tttggataag agtcttatct tcggcactct tgactctagc cttaacttta 420

```
gatttctatt ccagaatacc tctcatatct atcttaaaac ctaaganggg taaagangtc 480
ataagattgt agtatgaaag antttgctta gttaaattat atctcaggaa actcattcat 540
ctacaaatta aattgtaaaa tgatggtttg ttgtatctga aaaaatgttt agaacaagaa 600
atgtaactgg gtacctgtta tatcaaagaa cctcnattta ttaagtctcc tcatagccan 660
atccttatat ngccctctct gacctgannt aatananact tgaataatga atagttaatt 720
taggnntggg c 731
```

<210> 47

<211> 640

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 5, 28, 106, 153, 158, 173, 176, 182, 189, 205, 210, 214,
225, 226, 229, 237, 260, 263, 269, 277, 281, 282, 322, 337,
338, 354, 365, 428, 441, 443, 456, 467, 476, 484, 503, 508,
554, 567, 575, 579, 588, 601, 606, 609, 611, 621, 636

<223> n = A,T,C or G

<400> 47

```
tgcgngccgg tttggccctt ctttgtanga cactttcatc cgccctgaaa tcttcccgat 60
cgttaataac tcttcaggtc cctgcctgca cagggttttt tcttantttg ttgcctaaca 120
gtacaccaaa tgtgacatcc tttcaccaat atngattnct tcataccaca tcntonatgg 180
anacgactnc aacaattttt tgatnaccn aaanactggg ggctnnaana agtacctct 240
ggagcagcat ggacctgtcn gcnactaang gaacaanagt nntgaacatt tacacaacct 300
ttggtatgtc ttactgaaag anagaaacat gcttctncc ctagaccacg aggncaaccg 360
caganattgc caatgccaag tccgagcggg tagatcaggg aatacattcc atggatgcat 420
tacatacntt gtccccgaaa nanaagatgc cctaanggct tcttcanact ggtcongaaa 480
acancacac ctggtgcttg ganaacanac tctttggaag atcatctggc acaagttccc 540
cccagtggtt tttnccttgg cacctancct accanacna ttcggaancc attctttgcc 600
ntggcnttnt nttgggacca ntcttctcac aactgnacc 640
```

<210> 48

<211> 257

<212> DNA

<213> Homo sapiens

<400> 48

```
actagtatat gaaaatgtaa atatcacttg tgtactcaaa caaaagttgg tcttaagctt 60
ccaccttgag cagccttgga aacctaacct gcctctttta gcataatcac attttctaaa 120
tgattttctt tgttcctgaa aaagtgattt gtattagttt tacatttgtt ttttggaaga 180
ttatatattg atatgtatca tcataaaata tttaaataaa aagtatcttt agagtgaaaa 240
aaaaaaaaa aaaaaaa 257
```

<210> 49

<211> 652

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 410, 428, 496, 571, 647

<223> n = A,T,C or G

<400> 49

```
actagttcag atgagtggtt gctgaagggg ccccttgtc attttcatta taaccaatt 60
tccacttatt tgaactctta agtcataaat gtataatgac ttatgaatta gcacagttaa 120
```

```

gttgacacta gaaactgcc atttctgtat tacactatca aataggaac attggaaaga 180
tggggaaaaa aatcttattt taaaatggct tagaaagttt tcagattact ttgaaaattc 240
taaaacttctt tctgtttcca aaacttgaaa atatgtagat ggactcatgc attagactg 300
ttttcaaaagc tttcctcaca tttttaaagt gtgattttcc ttttaataata catatttatt 360
ttctttaaag cagctatata ccaacccatg actttggaga tatacctatn aaaccaatat 420
aacagcangg ttattgaagc agctttctca aatgttgctt cagatgtgca agttgcaaat 480
tttattgtat ttgtanaata caatttttgt tttaaactgt atttcaatct atttctccaa 540
gatgcttttc atatagagtg aaatatccca ngataactgc ttctgtgtcg tcgcatttga 600
cgcataactg cacaaatgaa cagtgtatac ctcttggttg tgcattnacc cc 652

```

<210> 50

<211> 650

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 237, 270, 311, 443, 454, 488, 520, 535, 539, 556, 567, 594, 603, 634

<223> n = A,T,C or G

<400> 50

```

ttgcgctttg attttttttag ggcttgtgcc ctgtttcact tatagggtct agaatgcttg 60
tgttgagtaa aaaggagatg cccaatattc aaagctgcta aatgttctct ttgccataaa 120
gactccgtgt aactgtgtga acacttgga tttttctcct ctgtcccgag gtcgtcgtct 180
gctttctttt ttgggttctt tctagaagat tgagaaatgc atatgacagg ctgagancac 240
ctccccaac acacaagctc tcagccacan gcagcttctc cacagcccca gcttcgcaca 300
ggctcctgga nggctgcctg ggggaggcag acatgggagt gccaaagggtg ccagatgggt 360
ccaggactac aatgtcttta tttttaactg tttgccactg ctgccctcac ccctgcccg 420
ctctggagta ccgtctgccc canacaagtg ggantgaaat ggggggtggg gggaacactg 480
attcccantt aggggggtgcc taactgaaca gtagggatan aaggtgtgaa cctgngaant 540
gcttttataa attatnttcc ttgttanatt tattttttta tttaatctct gttnaactgc 600
cnggggaaaa ggggaaaaaa aaaaaaaaaa tctnttttaa cacatgaaca 650

```

<210> 51

<211> 545

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 66, 159, 195, 205, 214, 243, 278, 298, 306, 337, 366, 375, 382, 405, 446, 477, 492, 495, 503, 507, 508, 521, 537

<223> n = A,T,C or G

<400> 51

```

tggcgtgcaa ccagggtagc tgaagtttg gtctgggact ggagattggc cattaggcct 60
cctganattc cagctccctt ccaccaagcc cagtcttgct acgtggcaca gggcaaacct 120
gactcccttt gggcctcagt ttccctctcc cttcatgana tgaaaagaat actactttt 180
cttgttggtc taacnttgct ggacncaaag tgtngtcatt attgttgat tgggtgatgt 240
gtncaaaact gcagaagctc actgcctatg agaggaanta agagagatag tggatganag 300
ggacanaagg agtcattatt tggtagatg ccacccntcc caacctttct ctctcagtc 360
cctgcncttc atgtntctgg tntgtgagt cctttgtgcc accanccatc atgctttgca 420
ttgctgcat cctgggaagg ggggtgnatc tctcacaact tgttgcacg gtttganatg 480
catgctttct tnatnaaaca aanaaanaa tgtttgacag ngtttaaaat aaaaaanaa 540
caaaa
545

```

<210> 52

<211> 678
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 98, 119, 121, 131, 136, 139, 140, 142, 143, 163, 168, 172,
176, 184, 189, 190, 191, 200, 201, 205, 207, 221, 223, 229,
230, 237, 240, 241, 255, 264, 266, 267, 276, 280, 288, 289,
291, 297, 301, 306, 308, 314, 315, 326, 332, 335, 337
<223> n = A,T,C or G

<221> misc_feature
<222> 339, 341, 343, 344, 345, 347, 350, 355, 356, 358, 362, 363,
372, 379, 395, 397, 398, 400, 403, 412, 414, 421, 423, 431,
435, 438, 439, 450, 457, 463, 467, 471, 474, 480, 483, 484,
487, 490, 491, 492, 493, 499, 500, 504, 508, 518, 536
<223> n = A,T,C or G

<221> misc_feature
<222> 538, 549, 551, 552, 554, 556, 557, 562, 563, 567, 571, 572,
576, 579, 590, 592, 595, 598, 606, 609, 613, 620, 622, 624,
626, 631, 634, 638, 641, 647, 654, 660, 661, 674
<223> n = A,T,C or G

<400> 52
actagtagaa gaactttgcc gcttttgtgc ctctcacagg cgcctaaagt cattgccatg 60
ggaggaagac gatttggggg gggagggggg gggggcangg tccgtggggc tttccctant 120
ntatctccat ntccantggn cnntgtcgcc ttttccctcg tcncattnga anttantccc 180
tggnccecn nccctctccn nectnccct ccccccctcg ncnccctcnn cttttntan 240
ncttcccat ctccntcccc cctnanngtc ccaacnccgn cagcaatnnc ncaactnctc 300
nctccnccc tcnnccgtt cttctnttct cnactntnnc ncnmntnccn tgccnntnaa 360
annctctccc cncgtcaanc gattctctcc ctccnccnnan ctntccactc cntncttctc 420
ncnccgtctc ntntctnnc ccacctctcn ccttcgnccc cantacnctc nccncccttn 480
cgntcattt nntcctcnn accnccncc tcccttccncc cctcttctcc ccggtntntc 540
tctctccnnc nncnccncc cncnccntcc nngcgnccnt ttccgccccn cncnccntt 600
ccttctncc cantccatcn cntntnccat nctnccncc nctcacnccc gctncccccn 660
ntctctttca cacngtcc 678

<210> 53
<211> 502
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 139, 146, 215, 217, 257, 263, 289, 386, 420, 452, 457, 461,
466, 482, 486
<223> n = A,T,C or G

<400> 53
tgaagatcct ggtgtcgcca tgggcccgcg ccccgcccggt tgttaccggt attgtaagaa 60
caagccgtac ccaaagtctc gcttctgcg aggtgtccct gatgccaaa ttcgcatttt 120
tgacctgggg cggaaaaang caaaantgga tgagtctccg ctttgtggcc acatgggtgc 180
agatcaatat gacgagctgt cctctgaagc cctgnangct gccgaattt gtgccaataa 240
gtacatggta aaaagtngtg gcnaagatgc ttccatatcc ggggtcggnnt ccaccccttc 300
cacgtcatcc gcatcaacaa gatgttgtcc tgtgtctggg ctgacaggct cccaacaggc 360
atgcgaagtg cctttggaaa acccanggca ctgtggccag gggtcacatt gggccaattn 420

atcatgttca tccgcaccaa ctgcagaaca angaaentgt naattnaagc cctgcccagg 480
gncaanttca aatttcccgg cc 502

<210> 54
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 431, 442, 445
<223> n = A,T,C or G

<400> 54
actagtccaa gaaaaaatatg cttaatgtat attacaaagg ctttgtatat gttaacctgt 60
tttaatgccaa aaagtgttgct ttgtccacaa ttcccttaag acctcttcag aaagggattt 120
gtttgcctta atgaatactg ttgggaaaaa acacagtata atgagtgaag agggcagaag 180
caagaaattt ctacatctta gcgactccaa gaagaatgag tatccacatt tagatggcac 240
attatgagga ctttaatctt tccttaaaaca caataatgtt ttcttttttc ttttattcac 300
atgatttcta agtatatttt tcatgcagga cagtttttca accttgatgt acagtgactg 360
tggttaaattt ttctttcagt ggcaacctct ataactctta aaatatggtg agcatcttgt 420
ctgttttgaa ngggatatga cnatnaatct atcagatggg aaatcctggt tccaagttag 480
aaaaaaaaaaaa aaaa 494

<210> 55
<211> 606
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 375, 395, 511, 542, 559, 569, 578, 581
<223> n = A,T,C or G

<400> 55
actagtaaaa agcagcattg ccaaataatc cctaattttc cactaaaaat ataataaat 60
gatgttaagc tttttgaaaa gtttaggtta aacctactgt tgtagatta atgtatttgt 120
tgcttccctt tatctggaat gtggcattag cttttttatt ttaacctctt ttaattctta 180
ttcaattcca tgacttaagg ttggagagct aaacactggg atttttggat aacagactga 240
cagttttgca taattataat cggcattgta catagaaagg atatggctac cttttgttaa 300
atctgcactt tctaaatata aaaaaaggga aatgaagtat aaatcaattt ttgtataatc 360
tgtttgaaac atgantttta ttgtcttaat attanggctt tgcccttttc tgtagtctc 420
ttgggatcct gtgtaaaact gttctcatta aacaccaaac agttaagtcc attctctggt 480
actagctaca aattccgttt catattctac ntaacaattt aaattaactg aaatatttct 540
anatggtcta cttctgtcnt ataaaaacna aacttgantt nccaaaaaaa aaaaaaaaaa 600
aaaaaa 606

<210> 56
<211> 183
<212> DNA
<213> Homo sapiens

<400> 56
actagtatat ttaaaccttac aggcattattt gtaatgtaaa ccaccatttt aatgtactgt 60
aattaacatg gttataatac gtacaatcct tccctcatcc catcacacaa ctttttttgt 120
gtgtgataaa ctgatttttg tttgcaataa aaccttgaaa aataaaaaaa aaaaaaaaaa 180
aaa 183

<210> 57
<211> 622
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 358, 368, 412, 414, 425, 430, 453, 455, 469, 475, 495, 499,
529, 540, 564, 575, 590
<223> n = A,T,C or G

<400> 57
actagtcaact actgtcttct ccttgtagct aatcaatcaa tattcttccc ttgcctgtgg 60
gcagtggaga gtgtgctggt gtgtacgctg cacctgcccc ctgagttggg gaaagaggat 120
aatcagtgag cactgttctg ctgagagctc ctgatctacc ccaccccta ggatccagga 180
ctgggtcaaa gctgcatgaa accaggccct ggcagcaacc tgggaatggc tggagggtgg 240
agagaacctg acttctcttt cctctccct cctccaacat tactggaact ctatcctgtt 300
agggatcttc tgagcttggt tccctgctgg gtgggacaga agacaaagga gaagggangg 360
tctacaanaa gcagcccttc tttgtcctct ggggttaatg agcttgacct ananttcatt 420
gaganaccan aagcctctga tttttaattt cntnaaatg tttgaagtnt atatntacat 480
atatatatat ctttnaatnt ttgagtcttt gatatgtctt aaaatccant cctctgcon 540
gaaacctgaa ttaaaaccat gaanaaaat gtttncctta aagatgttan taattaattg 600
aaacttgaaa aaaaaaaaaa aa 622

<210> 58
<211> 433
<212> DNA
<213> Homo sapiens

<400> 58
gaacaaattc tgattgggta tgtaccgtca aaagacttga agaaatttca tgattttgca 60
gtgtggaagc gttgaaaatt gaaagttact gcttttccac ttgctcatat agtaaaggga 120
tcctttcagc tgccagtgtt gaataatgta tcatccagag tgatgttata tgtgacagtc 180
accagcttta agctgaacca ttttatgaat accaaataaa tagacctott gtactgaaaa 240
catatttggt actttaatcg tgcgtcttgg atagaaatat ttttactggg tcttctgaat 300
tgacagtaaa cctgtccatt atgaatggcc tactgttcta ttatttgttt tgacttgaat 360
ttatccacca aagacttcat ttgtgtatca tcaataaagt tgtatgtttc aactgaaaaa 420
aaaaaaaaaa aaa 433

<210> 59
<211> 649
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 22, 190, 217, 430, 433, 484, 544, 550, 577, 583, 594
<223> n = A,T,C or G

<400> 59
actagttatt atctgacttt cnggttataa tcattctaata gagggtgaag tagcctctgg 60
tgtcatttgg atttgcatth ctctgatgag tgatgctatc aagcaccttt gctgggtgctg 120
ttggccatat gtgtatgttc cctggagaag tgcctgtgct gagccttggc ccacttttta 180
attaggcgtn tgccttttta ttactgagtt gtaaganttc tttatatatt ctggattcta 240
gacccttata agatacatgg ttgcaaata tttctccca ttctgtgggt tgtgttttca 300
ctttatcgat aatgtcctta gacatataat aaatttgtat tttaaaagt acttgatttg 360
ggctgtgcaa ggtgggtcca cgcttgtaat ccagcactt tgggagactg aggtgggtgg 420
atcatatgan gangctagga gttcgaggtc agcctggcca gcatagcgaa aacttgtctc 480

```
tacnaaaaaat acaaaaaatta gtcaggcatg gtggtgcacg tctgtaatac cagctttctca 540
ggangctgan gcacaaggat cacttgaacc ccagaangaa gangttgcag tganctgaag 600
atcatgccag ggcaacaaaa atgagaactt gtttaaaaaa aaaaaaaaaa 649
```

```
<210> 60
<211> 423
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 209, 222, 277, 389, 398
<223> n = A,T,C or G
```

```
<400> 60
actagttcag gccttccagt tcactgacaa acatggggaa gtgtgcccag ctggctggaa 60
acctggcagt gataccatca agcctgatgt ccaaaagagc aaagaatatt tctccaagca 120
gaagtgcgag ctgggctggt ttagtgccag gctgcggtgg gcagccatga gaacaaaacc 180
tcttctgtat ttttttttcc cattagtana acacaagact cngattcagc cgaattgtgg 240
tgtctttacaa ggcagggtct tctacagggt ggtgganaaa acagcctttc ttccctttgtt 300
aggaatggcc tgagttggcg ttgtgggcag gctactggtt tgtatgatgt attagtagag 360
caaccattta atcttttgta gtttgatna aacttgantc gagaccttaa acaaaaaaaa 420
aaa 423
```

```
<210> 61
<211> 423
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 195, 285, 295, 329, 335, 340, 347, 367, 382, 383, 391, 396,
418
<223> n = A,T,C or G
```

```
<400> 61
cgggactgga atgtaaagtg aagttcggag ctctgagcac gggctcttcc cgccgggtcc 60
tccctcccca gacccagag ggagaggccc accccgccc gcccgcgcc agccctgct 120
caggtctgag tatggctggg agtcgggggc cacaggcctc tagctgtgct gctcaagaag 180
actggatcag ggtanctaca agtgccggg ccttgccctt gggattctac cctgttccca 240
atttggtggt ggggtgcggg gtccttgccc cccttttcca cactncctcc ctcngacag 300
caacctccct tggggcaatt gggcctggnt ctcncccgnt tgttgcnaac ctttgttgg 360
ttaaggncct taaaaatggt annntttccc ntgccnggt taaaaaagga aaaaactnaa 420
aaa 423
```

```
<210> 62
<211> 683
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> 218, 291, 305, 411, 416, 441, 443, 453, 522, 523, 536, 542,
547, 566, 588, 592, 595, 603, 621, 628, 630, 632, 644, 645,
648, 655, 660, 672, 674, 676, 677, 683
<223> n = A,T,C or G
```

```
<400> 62
```

```

gctggagagg ggtacggact ttcttgaggt tgtcccaggt tggaatgaga ctgaactcaa 60
gaagagaccc taagagactg gggaatggtt cctgccttca ggaaagtga agacgcttag 120
gctgtcaaca cttaaaggaa gtccccttga agcccagagt ggacagacta gaccattga 180
tgggggccact ggccatggtc cgtggacaag acattccngt gggccatggc acaccggggg 240
ggatcaaaat gtgtacttgt ggggtctcgc cccttgccaa aaccaaacca ntcccactcc 300
tgtcnttggga ctttcttccc attccctcct ccccaaatgc acttcccctc ctccctctgc 360
ccctcctgtg tttttggaat tctgtttccc tcaaaattgt taatttttta nttttngacc 420
atgaacttat gtttggggtc nangttcccc ttnccaatgc atactaatat attaatggtt 480
atattttttt gaaatatttt ttaatgaact tggaaaaaat tnntggaatt tccttncttc 540
cnttttnttt ggggggggtg gggggntggg ttaaaatttt tttggaancc cnatnggaaa 600
ttnttacttg gggccccctc naaaaaantn anttccaatt cttnnatngc ccctnttccn 660
ctaaaaaaaa ananannaaa aan 683

```

<210> 63

<211> 731

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 237, 249, 263, 288, 312, 317, 323, 326, 337, 352, 362, 370, 377, 400, 411, 414, 434, 436, 446, 457, 473, 486, 497, 498, 502, 512, 531, 546, 554, 563, 565, 566, 588, 597, 608, 611, 613, 615, 627, 632, 640, 641, 644, 654, 660, 663, 665

<223> n = A,T,C or G

<221> misc_feature

<222> 671, 678, 692, 697, 698, 699, 704, 705, 712, 714, 717, 718, 719, 723, 725, 730, 731

<223> n = A,T,C or G

<400> 63

```

actagtcata aagggtgtgc gcgtcttcga cgtggcggtc ttggcgccac tgctgcgaga 60
ccgggccctg gacctcaagg tcatccactt ggtgcgtgat ccccgcgcgg tggcgagttc 120
acggatccgc tcgcgccacg gcctcatccg tgagagccta cagggtggtg gcagccgaga 180
ccgcgagctc accgcatgcc cttcttgag gcccggggcc acaagcttgg cgcccanaaa 240
gaaggcgtng gggggccgca aantaccacg ctctgggcgc tatggaangt cctcttgcaa 300
taatattggt tnaaaanctg canaanagcc cctgcancct cctgaactgg gntgcagggc 360
cncttacctn gtttggtg ggttacaaag aacctgtttn ggaaaaccct nccnaaaacc 420
ttccgggaaa attntncaaa ttttntttgg ggaattnttg ggtaaaaccc ccnaaaatgg 480
gaaacntttt tgccctnnaa antaaaccat tnggttccgg gggccccccc ncaaaaccct 540
ttttnttttt tttntgcccc cantnncccc ccggggcccc ttttttntgg ggaaaanccc 600
ccccctnccc nanantttta aaaggngggg anaatttttn nttnccccc gggncccccn 660
ggngntaaaa nggtttcncc cccccgagg gnggggnnnc ctcnnaaacc cntntcnna 720
ccncttttn n 731

```

<210> 64

<211> 313

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 240

<223> n = A,T,C or G

<400> 64

```

actagttgtg caaaccacga ctgaagaaag acgaaaagtg ggaaataact tgcaacgtct 60

```

```
gtagagatg gttgctacac atgttgggtc ttagagaaaa catcttgagg agcagattgc 120
taaagttgat agagaatatg aagaatgcat gtcagaagat ctctcggaaa atattaaaga 180
gattagagat aagtatgaga agaaagctac tctaattaag tcttctgaag aatgaagatn 240
aaatgttgat catgtatata tatccatagt gaataaaatt gtctcagtaa agttgtaaaa 300
aaaaaaaaaa aaa 313
```

<210> 65

<211> 420

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 400, 402, 403, 404, 405, 406, 409, 411, 412, 414, 415, 416

<223> n = A,T,C or G

<400> 65

```
actagttccc tggcaggcaa gggcttccaa ctgaggcagt gcatgtgtgg cagagagagg 60
caggaagctg gcagtggcag cttctgtgtc tagggagggg tgtggctccc tccttccttg 120
tctgggaggt tggagggaag aatctaggcc ttagcttgcc ctccctgccac ccttcccctt 180
gtagatactg ccttaacact ccctcctctc tcagctgtgg ctgccaccca agccaggttt 240
ctccgtgctc actaatttat ttccaggaaa ggtgtgtgga agacatgagc cgtgtataat 300
atttgtttta acattttcat tgcaagtatt gaccatcatc cttgggttggt tatcgttgta 360
acacaaatta atgatattaa aaagcatcca aacaaagccn annnnnaana nnannngaaa 420
```

<210> 66

<211> 676

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 328, 454, 505, 555, 586, 612, 636, 641

<223> n = A,T,C or G

<400> 66

```
actagtttcc tatgatcatt aaactcatto tcagggttaa gaaaggaatg taaatttctg 60
cctcaatttg tacttcatca ataagttttt gaagagtgcg gatttttagt caggtcttaa 120
aaataaaactc acaaatctgg atgcatttct aaattctgca aatgtttcct ggggtgactt 180
aacaagggaat aatcccacaa tatacctagc tacctaatac atggagctgg ggctcaacc 240
actgttttta aggatttgcg cttacttggt gctgaggaaa aataagtagt tccgagggaa 300
gtagttttta aatgtgagct tatagatngg aaacagaata tcaacttaat tatggaaatt 360
gttagaaaacc tgttctcttg ttatctgaat cttgattgca attactattg tactggatag 420
actccagccc attgcaaagt ctcatatc ttanctgtgt agttgaattc cttggaaatt 480
ctttttaaga aaaaattgga gtttnaaaga aataaaccct tttgttaaatt gaagcttggc 540
tttttggtga aaanaaatca tcccgagggt cttattgttt aaaaanggaa ttttaagcct 600
ccctggaaaa anttgttaat taaatgggga aaatgntggg naaaaattat ccgttagggt 660
ttaaaggga aactta 676
```

<210> 67

<211> 620

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 419, 493, 519, 568, 605, 610

<223> n = A,T,C or G

<400> 67

```
caccattaaa gctgcttacc aagaacttcc ccagcatttt gacttccttg tttgatagct 60
gaattgtgag caggtgatag aagagccttt ctagttgaac atacagataa tttgctgaat 120
acattccatt taatgaagg gttacatctg ttacgaagct actaagaagg agcaagagca 180
taggggaaaa aaatctgac agaacgcac aaactcacat gtgccccctc tactacaaac 240
agattgtagt gctgtggttg tttattccgt tgtgcagaac ttgcaagctg agtcactaaa 300
cccaaagaga ggaaattata ggtagttaa acattgtaat cccaggaact aagtttaatt 360
cacttttgaa gtgttttgtt ttttattttt ggtttgtctg atttactttg ggggaaaang 420
ctaaaaaaa agggatatca atctctaatt cagtgccac taaaagttgt ccctaaaaag 480
tctttactgg aanttattgg actttttaag ctccaggtnt tttggtcctc caaattaacc 540
ttgcatgggc cccttaaaat tgttgaangg cattcctgcc tctaagtttg gggaaaattc 600
ccccnttttn aaaatttgga 620
```

<210> 68

<211> 551

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 286, 464, 480, 501, 502, 518, 528, 533, 536, 537, 538, 539,
540, 541, 543, 544, 545, 547, 548, 549

<223> n = A,T,C or G

<400> 68

```
actagtagct ggtacataat cactgaggag ctatttctta acatgctttt atagaccatg 60
ctaagtctag accagtattt aagggtctaat ctacacacct cttagctgta agagtctggc 120
ttagaacaga cctctctgtg caataacttg tggccactgg aaatccctgg gccggcattt 180
gtattggggt tgcaatgact cccaagggcc aaaagagtta aaggcacgac tgggatttct 240
tctgagactg tggtgaaact ccttccaagg ctgagggggt cagtangtgc tctgggaggg 300
actcggcacc actttgatat tcaacaagcc acttgaagcc caattataaa attgttattt 360
tacagctgat ggaactcaat ttgaaccttc aaaactttgt tagtttatcc tattatattg 420
ttaaacctaa ttacatttgt ctagcattgg atttggttcc tgtngcatat gtttttttcn 480
cctatgtgct ccctccccc nnatcttaat taaaccnca attttgcnat tcnccnnnnn 540
nanannanna a 551
```

<210> 69

<211> 396

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 235, 310, 323, 381

<223> n = A,T,C or G

<400> 69

```
cagaaatgga aagcagagtt ttcatttctg tttataaacg tctccaaaca aaaatggaaa 60
gcagagtttt cattaaatcc ttttaccttt tttttttctt ggtaatcccc tcaaataaca 120
gtatgtggga tattgaatgt taaagggata tttttttcta ttatttttat aattgtacaa 180
aattaagcaa atgttaaaag ttttatatgc tttattaatg ttttcaaaag gtatnatata 240
tgtgatcat tttttaagct tcagttgctt gtcttctggt actttctggt atgggctttt 300
ggggagccan aaaccaatct acnatctctt tttgtttgcc aggacatgca ataaaattta 360
aaaaataaat aaaactatt nagaattga aaaaaa 396
```

<210> 70

<211> 536
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 388, 446, 455
<223> n = A,T,C or G

<400> 70
actagtgc aaagcaaatat aaacatcgaa aaggcggttc tcacgttagc tgaagatata 60
cttcgaaaga cccctgtaaa agagcccaac agtgaaaatg tagatatcag cagtggagga 120
ggcgtgacag gctggaagag caaatgctgc tgagcattct cctgttccat cagtggccat 180
ccactacccc gttttctctt cttgctgcaa aataaaccac tctgtccatt ttttaactcta 240
aacagatatt tttgtttctc atcttaacta tccaagccac ctattttatt tgttctttca 300
tctgtgactg cttgctgact ttatcataat tttcttcaaa caaaaaaatg tatagaaaaa 360
tcatgtctgt gacttcattt ttaaagtnta cttgtcagc tcaactgcat ttcagttgtt 420
ttatagtcca gttcttatca acattnaaac ctatngcaat catttcaaat ctattctgca 480
aattgtataa gaataaaagt tagaatttaa caattaaaaa aaaaaaaaaa aaaaaa 536

<210> 71
<211> 865
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 22, 35, 39, 56, 131, 138, 146, 183, 194, 197, 238, 269, 277,
282, 297, 316, 331, 336, 340, 341, 346, 349, 370, 376, 381,
382, 392, 396, 397, 401, 433, 444, 445, 454, 455, 469, 472,
477, 480, 482, 489, 497, 499, 511, 522, 526, 527
<223> n = A,T,C or G

<221> misc_feature
<222> 545, 553, 556, 567, 574, 580, 610, 613, 634, 638, 639, 663,
672, 689, 693, 694, 701, 704, 713, 723, 729, 732, 743, 744,
749, 761, 765, 767, 769, 772, 774, 780, 783, 788, 792, 803,
810, 824, 840, 848
<223> n = A,T,C or G

<400> 71
gacaaagcgt taggagaaga anagaggcag ggaanactnc ccaggcacga tggccncctt 60
cccaccagca accagcgccc cccaccagcc cccaggcccc gacgacgaag actccatcct 120
ggattaatct nacctctntc gcctgnccca ttctacctc ggaggtggag gcoggaagg 180
tcnaccacag aganaanctg ctgccaacac caaccgcccc agccctggcg ggcacganag 240
gaaactggtg accaatctgc agaattctna gaggaanaag cnaggggccc cgcgctnaga 300
cagagctgga tatgangcca gaccatggac nctacnccn ncaatncana cgggactgcg 360
gaagatggan gaccncgac nngatcaggc cngctnncca nccccccacc cctatgaatt 420
attcccgctg aangaatctc tgannngcct ccannaaagc gcctccccnc cnaacgnaan 480
tncaacatng ggattanang ctgggaactg naaggggcaa ancctnnaat atccccagaa 540
acaanctctc ccnaanaaac tggggcncct catnggtggn accaactatt aactaaaccg 600
cacgccaagn aantataaaa ggggggcccc tcncggnng accccctttt gtcccttaat 660
ganggttatc cnccttgctg accatggtnc ccnnttctgt ntgnatgttt ccnctcccct 720
ccncttatnt cnagccgaac tcnnatttnc cggggggtgc natcnantng tncncctttn 780
ttngttgncc cngcccttcc cngcggaacn cgtttccccc ttantaacgg caccgggggn 840
aagggtgntt ggccccctcc ctccc 865

<210> 72

<211> 560
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 83, 173, 183, 186, 209, 211, 215, 255, 321, 322, 323, 335,
344, 357, 361, 368, 394, 412, 415, 442, 455, 469, 472, 475,
487, 513, 522, 528, 531, 534, 546
<223> n = A,T,C or G

<400> 72
cctggacttg tcttggttcc agaacctgac gacccggcga cggcgacgtc tcttttgact 60
aaaagacagt gtccagtgtc ccngcctagg agtctacggg gaccgcctcc cgcgccgcca 120
ccatgcccaa cttctctggc aactggaaaa tcatccgacg ggaaaacttc gangaattgc 180
tcnaantgct gggggtgaat gtgatgctna ngaanattgc tgtggctgca gcgtccaagc 240
cagcagtgga gatcnaacag gagggagaca ctttctacat caaaacctcc accaccgtgc 300
gcaccacaaa gattaacttc nnngttgggg aggantttga ggancaaaact gtggatngga 360
ngcctgtnaa aacctggtga aatgggagaa tganaataaa atggtctgtg ancanaaact 420
cctgaaaagga gaaggccccc anaactcctg gaccngaaaa actgaccncn cnatngggga 480
actgatnctt gaacctgaa cgggcgggat ganccttttt tnttgcncnc naanggggtc 540
tttccntttc cccaaaaaaa 560

<210> 73
<211> 379
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 8, 17, 18, 21, 26, 29, 30, 32, 53, 56, 67, 71, 81, 102, 104,
111, 112, 114, 119, 122, 124, 125, 134, 144, 146, 189, 190,
214, 215, 219, 220, 235, 237, 246, 280, 288, 302, 310, 313,
319, 322, 343, 353, 354
<223> n = A,T,C or G

<400> 73
ctggggancc ggcggtnncc nccatntcnn gncgcgaagg tggcaataaa aancnctga 60
aaccgcncaa naacatgcc naagatatgg acgaggaaga tngngctttc nngnacaanc 120
gnannagga acanaacaaa ctcnangagc tctcaagcta atgccgcggg gaaggggccc 180
ttggccacnn gtggaattaa gaaatctggc aaanngtann tgttccttgt gcctnangag 240
ataagngacc ctttatttca tctgtattta aacctctctn ttccctgnca taacttcttt 300
tnccacgtan agntggaant anttgtgtgc ttggactgtt gtncatttta gannaaactt 360
ttgttcaaaa aaaaaataa 379

<210> 74
<211> 437
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 145, 355
<223> n = A,T,C or G

<400> 74
actagttcag actgccacgc caaccccaga aaatacccca catgccagaa aagtgaagtc 60
ctaggtgttt ccatctatgt ttcaatctgt ccatctacca ggctcgcga taaaaacaaa 120

```

acaaaaaac gctgccaggt tttanaagca gttctgggtct caaaaccatc aggatcctgc 180
caccagggtt cttttgaaat agtaccacat gtaaaaagga atttggcttt cacttcacat 240
aatcactgaa ttgtcaggct ttgattgata attgtagaaa taagtagcct tctgttgg 300
gaataagtta taatcagtat tcatctcttt gttttttgtc actcttttct ctctnattgt 360
gtcatttgta ctgtttgaaa aatatttctt ctataaaatt aaactaacct gccttaaaaa 420
aaaaaaaaa aaaaaaa 437

```

```

<210> 75
<211> 579
<212> DNA
<213> Homo sapiens

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```

<220>
<221> misc_feature
<222> 440, 513, 539, 551
<223> n = A,T,C or G

```

```

<400> 75
ctccgtcgcc gccaatgata tgtgcggggc gccctccgcc acgcagccgg ccaccgccga 60
gacccagcac atcgccgacc aggtgaggtc ccagcttgaa gagaaagaaa acaagaagtt 120
ccctgtgttt aaggccgtgt cattcaagag ccagggtgtc gcggggacaa actacttcat 180
caaggtgcac gtcggcgacg aggacttctg acacctgcga gtgttccaat ctctccctca 240
tgaaaacaag cccttgacct tatctaacta ccagaccaac aaagccaagc atgatgagct 300
gacctatttc tgatcctgac tttggacaag gcccttcagc cagaagactg acaaagtcac 360
cctccgtcta ccagagcgtg cacttgtgat cctaaaataa gcttcacctc cggtgtgtgc 420
ccttgggggtg gaaggggcan gatctgact gcttttgcat ttctcttctt aaatttcatt 480
gtgttgattc tttccttcca ataggtgatc ttnattactt tcagaatatt ttccaaatna 540
gatataatctt naaaatcctt aaaaaaaaaa aaaaaaaaaa 579

```

```

<210> 76
<211> 666
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 411, 470, 476, 491, 506, 527, 560, 570, 632, 636, 643, 650,
654, 658
<223> n = A,T,C or G

```

```

<400> 76
gtttatccta tctctccaac cagattgtca gctccttgag ggcaagagcc acagtatatt 60
tccctgtttc ttccacagtg cctaataata ctgtggaact aggttttaat aattttttaa 120
ttgatgttgt tatgggcagg atggcaacca gaccattgtc tcagagcagg tgctggctct 180
ttcctggcta ctocagtgt gctagcctct ggtaacctct tacttattat cttcaggaca 240
ctcactacag ggaccaggga tgatgcaaca tccttgtctt tttatgacag gatgtttgct 300
cagcttctcc aacaataaaa agcacgtggt aaaacacttg cggatattct ggactgtttt 360
taaaaaatat acagtttacc gaaaatcata ttatcttaca atgaaaagga ntttatagat 420
cagccagtga acaacctttt cccaccatac aaaaattcct tttcccgaa gaaaanggct 480
ttctcaataa ncctcacttt cttaanatct tacaagatag ccccganac ttatcgaac 540
tcatttttagg caaatatgan ttttattgtg cgttacttgt ttcaaaattt ggtattgtga 600
atatcaatta ccaccccat ctcccatgaa anaaanggga aanggtgaan ttcntaancg 660
cttaaa 666

```

```

<210> 77
<211> 396
<212> DNA
<213> Homo sapiens

```

<220>
<221> misc_feature
<222> 31, 54, 125, 128, 136, 163, 168, 198
<223> n = A,T,C or G

<400> 77
ctgcagcccg ggggatccac taatctacca nggttatttg gcagctaatt ctanatttgg 60
atcattgccc aaagttgcac ttgctggtct cttgggattt ggccttggaa aggtatcata 120
catanganta tgccanaata aattccattt ttttgaaaat canctccntg gggctgggtt 180
tggtccacag cataacangc actgcctcct tacctgtgag gaatgcaaaa taaagcatgg 240
attaagtgag aagggagact ctcagccttc agcttcctaa attctgtgtc tgtgactttc 300
gaagtttttt aaacctctga atttgtacac atttaaaatt tcaagtgtac tttaaaataa 360
aatacttcta atgggaacaa aaaaaaaaaa aaaaaa 396

<210> 78
<211> 793
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 309, 492, 563, 657, 660, 703, 708, 710, 711, 732, 740, 748,
758, 762, 765, 787
<223> n = A,T,C or G

<400> 78
gcacccctagc cgccgactca cacaaggcag gtgggtgagg aaatccagag ttgccatgga 60
gaaaattcca gtgtcagcat tcttgctcct tgtggccctc tcctacactc tggccagaga 120
taccacagtc aaacctggag ccaaaaagga cacaaaggac tctcgaccca aactgcccc 180
gacctctccc agaggttggg gtgaccaact catctggact cagacatatg aagaagctct 240
atataaatcc aagacaagca acaaacccctt gatgattatt catcacttgg atgagtggcc 300
acacagtcna gctttaaaga aagtgtttgc tgaaaaataa gaaatccaga aattggcaga 360
gcagtttgtc ctccctcaatc tggtttatga acaactgac aaacaccttt ctccctgatgg 420
ccagtatgtc ccaggattat gtttgttgac ccatctctga cagttgaagc cgatatcctg 480
ggaagatatt cnaaccgtct ctatgcttac aaactgcaga taogctctgt tgcttgacac 540
atgaaaaagc tctcaagtgt ctnaaaatga attgtaagaa aaaaaatctc cagccttctg 600
tctgtcggct tgaaaattga aaccagaaaa atgtgaaaaa tggctattgt ggaacanatn 660
gacacctgat taggttttgg ttatgttcac cactattttt aanaaaanan nttttaaata 720
ttggttcaat tntctttttn aaacaatntg tttctacntt gnganctgat ttctaaaaaa 780
aataatnttt ggc 793

<210> 79
<211> 456
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 89, 195, 255, 263, 266, 286, 353, 384, 423, 425, 436, 441
<223> n = A,T,C or G

<400> 79
actagtatgg ggtgggaggg cccacccttc tcccctaggc gctgttcttg ctccaaaggg 60
ctccgtggag agggactggc agagctgang ccacctgggg ctggggatcc cactcttctt 120
gcagctgttg agcgaccta accactggtc atgcgccac ccctgctctc cgcacccgct 180
tctcccgac ccangacca ggctacttct cccctcctct tgccctccctc ctgcccctgc 240
tgccctctgat cgtangaatt gangantgtc ccgccttgtg gctganaatg gacagtggca 300

```

ggggctggaa atgggtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gnccccccc 360
tgcaagaccg agattgaggg aaancatgtc tgctgggtgt gaccatgttt cctctccata 420
aantnccctt gtgacnctca naaaaaaaaa aaaaaa 456

```

```

<210> 80
<211> 284
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 283
<223> n = A,T,C or G

```

```

<400> 80
ctttgtacct ctgaaaaaga taggtattgt gtcataaaac ttgagttaa attttatata 60
taaaactaaa agtaatgctc acttttagcaa cacatactaa aattggaacc atactgagaa 120
gaatagcatg acctccgtgc aaacaggaca agcaaatgtg tgatgtgttg attaaaaaga 180
aataaataaaa tgtgtatatg tgtaacttgt atgtttatgt ggaatacaga ttgggaaata 240
aatgtatttt ctactgtga aaaaaaaaaa aaaaaaaaaa aana 284

```

```

<210> 81
<211> 671
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 388, 505, 600, 603, 615, 642, 644, 660
<223> n = A,T,C or G

```

```

<400> 81
gccaccaaca ttccaagcta ccctgggtac ctttgtgcag tagaagctag tgagcatgtg 60
agcaagcggg gtgcacacgg agactcatcg ttataattta ctatctgcca agagtagaaa 120
gaaaggctgg ggatatttgg gttggcttgg ttttgatttt ttgcttgttt gtttgttttg 180
tactaaaaca gtattatctt ttgaatatcg tagggacata agtatataca tgttatccaa 240
tcaagatggc tagaatggtg cctttctgag tgtctaaaac ttgacacccc tggtaaatct 300
ttcaacacac ttccactgcc tgcgtaatga agttttgatt catttttaac cactggaatt 360
tttcaatgcc gtcattttca gttagatnat tttgcacttt gagattaaaa tgccatgtct 420
atttgattag tcttattttt ttattttttac aggccttatca gtctcactgt tggctgtcat 480
tgtgacaaag tcaaataaac cccnaggac aacacacagt atgggatcac atattgtttg 540
acattaagct ttggccaaaa aatgttgcag gtgttttacc tcgacttgct aaatcaatan 600
canaaaggct ggctnataat gttggtggtg aaataattaa tnantaacca aaaaaaaaaa 660
aaaaaaaaaa a 671

```

```

<210> 82
<211> 217
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 35
<223> n = A,T,C or G

```

```

<400> 82
ctgcagatgt ttcttgaatg ctttgtcaaa ttaanaaagt taaagtgcaa taatgtttga 60
agacaataag tgggtggtga tcttggttct aataagataa acttttttgt ctttgcttta 120

```

tcttattagg gagttgtatg tcagtgtata aaacatactg tgtggtataa caggcttaat 180
 aaattcttta aaaggaaaaa aaaaaaaaaa aaaaaaa 217

<210> 83
 <211> 460
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 104, 118, 172, 401, 422, 423, 444, 449
 <223> n = A,T,C or G

<400> 83
 cgcgagtggg agcaccagga tctcgggctc ggaacgagac tgcacggatt gttttaagaa 60
 aatggcagac aaaccagaca tgggggaaat cgccagcttc gatnaggcca agctgaanaa 120
 aacggagacg caggagaaga acaccctgcc gaccaaagag accattgagc angagaagcg 180
 gagtgaaatt tcctaagatc ctggaggatt tcctaccccc gtccctcttcg agaccccagt 240
 cgtgatgtgg aggaagagcc acctgcaaga tggacacgag ccacaagctg cactgtgaac 300
 ctgggcactc cgcgccgatg ccaccggcct gtgggtctct gaagggaccc cccccaatcg 360
 gactgccaaa ttctccggtt tgccccgga tattatacaa nattatttgt atgaataatg 420
 annataaaac acacctcgtg gcancaaana aaaaaaaaaa 460

<210> 84
 <211> 323
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 70, 138, 178, 197, 228, 242, 244, 287, 311
 <223> n = A,T,C or G

<400> 84
 tgggtggatct tggctctgtg gagctgctgg gacgggatct aaaagactat tctggaagct 60
 gtggtccaan gcattttgct ggcttaacgg gtcccgaac aaaggacacc agctctctaa 120
 aattgaagtt taccoganat aacaatcttt tgggcagaga tgcctatttt aacaaacncc 180
 gtccctgcgc aacaacnaac aatctctggg aaataccggc catgaacntg ctgtctcaat 240
 cnancatctc tctagctgac cgatcatatc gtcccagatt actacanatc ataataattg 300
 atttcctgta naaaaaaaaa aaa 323

<210> 85
 <211> 771
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 63, 426, 471, 497, 521, 554, 583, 586, 606, 609, 615, 652,
 686, 691, 694, 695, 706, 713, 730, 732, 743, 751
 <223> n = A,T,C or G

<400> 85
 aaactgggta ctcaacactg agcagatctg ttctttgagc taaaaacat gtgctgtacc 60
 aanagtttgc tcctggctgc tttgatgtca gtgctgctac tccacctctg cggcgaatca 120
 gaagcaagca actttgactg ctgtcttgga tacacagacc gtattcttca tcctaaattt 180
 attgtgggct tcacacggca gctggccaat gaaggctgtg acatcaatgc tatcatcttt 240
 cacacaaaga aaaagtgtgc tgtgtgcgca aatccaaaac agacttgggt gaaatatatt 300

```

gtgcgtctcc tcagtaaaaa agtcaagaac atgtaaaaaac tgtggctttt ctggaatgga 360
attggacata gccaagaac agaaagaact tgctgggggtt ggaggtttca ctgacacatc 420
atgganggtt tagtgcttat cttatttgtg cctcctggac ttgtccaatt natgaagtta 480
atcatattgc atcatanttt gctttgttta acatcacatt naaattaaac tgtattttat 540
gttatttata gctntaggtt ttctgtgttt aactttttat acnaantttc ctaaactatt 600
ttggtntant gcaanttaaa aattatattt ggggggggaa taaatattgg antttctgca 660
gccacaagct ttttttaaaa aaccantaca nccnngttaa atggtnggtc ccnaatggtt 720
tttgcttttn antagaaaat ttnttagaac natttgaaaa aaaaaaaaaa a 771

```

<210> 86
 <211> 628
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 162, 249, 266, 348, 407, 427, 488, 518, 545, 566, 569, 597,
 598, 611, 617, 621, 624
 <223> n = A,T,C or G

```

<400> 86
actagtttgc tttacatttt tgaaaagtat ttttttgtc caagtgttta tcaactaaac 60
cttgtgttag gtaagaatgg aatttattaa gtgaatcagt gtgacccttc ttgtcataag 120
attatcttaa agctgaagcc aaaatatgct tcaaaagaaa angactttat tggtcattgt 180
agttcatata ttcaaagcat ctgaactgta gtttctatag caagccaatt acatccataa 240
gtggagaang aaatagatta atgtcnaagt atgattggtg gagggagcaa ggttgaagat 300
aatctggggt tgaaattttc tagttttcat tctgtacatt ttaggttnga catcagattt 360
gaaatattaa tgtttacctt tcaatgtgtg gtatcagctg gactcantaa caccctttc 420
ttccctnggg gatggggaat ggattattgg aaaatggaaa gaaaaaagta cttaaagcct 480
tcctttcnca gtttctggct cctaccctac tgatttancc agaataagaa aacattttat 540
catcntctgc tttattccca ttaatnaant tttgatgaat aaatctgctt ttatgcnnac 600
ccaaggaatt nagtggnttc ntcnttgt 628

```

<210> 87
 <211> 518
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 384, 421, 486
 <223> n = A,T,C or G

```

<400> 87
ttttttattt tttttagaga gtagttcagc ttttatttat aaatttattg cctgttttat 60
tataacaaca ttatactgtt tatgttttaa tacatatggt tcaaaatgta taatacatca 120
agtagtacag ttttaaaatt ttatgcttaa aacaagtttt gtgtaaaaaa tgcagatata 180
ttttacatgg caaatcaatt tttaagtcac cctaaaaatt gatttttttt tgaaatttaa 240
aaacacattt aatttcaatt tctctcttat ataaccttta ttactatagc atggtttcca 300
ctacagttta acaatgcagc aaaattccca tttcacggtg aattgggttt taagcggcaa 360
ggttaaaatg ctttgaggat cctnaatacc ctttgacttt caaatgaagg ttatgggttg 420
naatttaacc ctcatgccat aagcagaagc acaagtttag ctgcattttg ctctaaactg 480
taaaancgag ccccccgttg aaaaagcaaa agggaccc 518

```

<210> 88
 <211> 1844
 <212> DNA
 <213> Homo sapiens

<400> 88

```

gagacagtga atcctagtat caaaggattt ttggcctcag aaaaagtgtg tgattatatt 60
tattttatatt tattttttcga gactccgtctt caaaaaaaaa aaaaaaaaaa agaatacaca 120
ggatatttgct aaagcatttt gagctgcttg gaaaaaggga agtagttgca gtagagtttc 180
ttccatcttc ttggtgctgg gaagccatat atgtgtcttt tactcaagct aaggggtata 240
agcttatgtg ttgaatttgc tacatctata ttccacatat tctcacaata agagaatttt 300
gaaatagaaa tatcatagaa catttaagaa agtttagtat aaataatatt ttgtgtgttt 360
taatcccttt gaagggatct atccaaagaa aatattttac actgagctcc ttcctacacg 420
tctcagtaac agatcctgtg ttagtctttg aaaatagctc attttttaaa tgtcagtggg 480
tagatgtagc atacatatga tgtataatga cgtgtattat gttacaatg tctgcagatt 540
ttgtaggaat acaaaacatg gcctttttta taagcaaaac gggccaatga ctagaataac 600
acatagggca atctgtgaat atgtattata agcagcattc cagaaaagta gttggtgaaa 660
taattttcaa gtcaaaaagg gatattggaa gggaattatg agtaacctct attttttaag 720
ctctgctttt aaattaaacg ctacagccat ttaagccttg aggataataa agcttgagag 780
taataatgtt aggttagcaa aggttagat gtatcacttc atgcatgcta ccatgatagt 840
aatgcagctc ttcgagtcac ttctggtcat tcaagatatt cacccttttg cccatagaaa 900
gcaccctacc tcacctgctt actgacattg tcttagctga tcacaagatc attatcagcc 960
tccattattc cttactgtat ataaaatata gagttttata ttttcccttc ttcgtttttc 1020
accatattca aaacctaaat ttgtttttgc agatggaatg caaagtaatc aagtgttcgt 1080
gctttcacct agaagggtgt ggtcctgaag gaaagaggtc cctaaatatc cccaccctg 1140
ggtgctcctc cttccctggt accctgacta ccagaagtca ggtgctagag cagctggaga 1200
agtgcagcag cctgtgcttc cacagatggg ggtgctgctg caacaaggct ttcaatgtgc 1260
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attgctcttc ctgctgctgt cctttgcttc tcaacggggc tcgctctaca gtctagagca 1380
catgcagcta acttgtgcct ctgcttatgc atgagggtta aattaacaac cataaccttc 1440
atttgaagtt caaagggtgta ttcaggatcc tcaaaagcatt ttaaccttgc cgcttaaaac 1500
ccaattttacc gtgaaatggg aattttgctg cattgttaaa ctgtagtggg aacctgcta 1560
tagtaataaa ggttatataa gagagaaatt gaaattaaat gtgtttttta atttcaaaaa 1620
aaaatcaatc tttaggatga cttaaaaatt gatttgccat gtaaaatgta tctgcatttt 1680
ttacacaaaaa cttgttttaa gcataaaatt ttaaaactgt actacttgat gtattataca 1740
ttttgaacca tatgtattaa accataaaca gtataatgtt gttataataa aacaggcaat 1800
aaattttata ataaaagctg aaaaaaaaaa aaaaaaaaaa aaaa 1844

```

<210> 89

<211> 523

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 288, 352, 369, 398, 475, 511, 513

<223> n = A,T,C or G

<400> 89

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tttttttttt tttttttagt caatccacat ttattgatca cttattatgt accaggcact 60
gggataaaga tgactgttag tcaactcagc taaggaagaa aactagcaaa taagacgatt 120
acaatatgat gtagaaaatg ctaagccaga gatatagaaa ggtcctattg ggtccttctg 180
tcaccttgtc tttccacatc cctacccttc acaggccttc cctccagctt cctgcccccg 240
ctccccactg cagatcccct gggattttgc cttagagctaa acgagganat gggccccctg 300
gccttgccat gacttgaacc caaccacaga ctgggaaagg gagccttttcg anagtggatc 360
actttgatna gaaaacacat aggggaattga agagaaantc cccaaatggc caccctgtgt 420
ggtgctcaag aaaagtgttc agaattggata aatgaaggat caagggaatt aatanatgaa 480
taattgaatg gtggctcaat aagaatgact ncnttgaatg acc 523

```

<210> 90

<211> 604

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 563

<223> n = A,T,C or G

<400> 90

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ccagtgtggt ggaatgcaaa gattaccccg gaagctttcg agaagctggg attccctgca 60
gcaaaggaaa tagccaatat gtgtcgtttc tatgaaatga agccagaccg agatgtcaat 120
ctcaccacc aactaaatcc caaagtcaaa agcttcagcc agtttatctc agagaaccag 180
gggagccttc aaggcatgt agaaaatcag ctgttcagat aggcctctgc accacacagc 240
ctctttcctc tctgatcctt ttctcttcta cggcacaaca ttcattgtttg acagaacatg 300
ctggaatgca attgtttgca acaccgaagg atttcctgcg gtcgcctctt cagttaggaag 360
cactgcattg gtgataggac acggtaattt gattcacatt taacttgcta gttagtata 420
aggggtggtt cactgtttt gtaaaatgag aagcctcgga aacttgggag cttctctcct 480
accactaatg gggaggcagc attattactg ggatttctcc tggggtgaat taatttcaag 540
ccctaattgc tgaaattccc ctnggcaggc tccagtttcc tcaactgcat tgcaaaattc 600
cccc 604
```

<210> 91

<211> 858

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 570, 591, 655, 664, 667, 683, 711, 759, 760, 765, 777, 787, 792, 794, 801, 804, 809, 817, 820

<223> n = A,T,C or G

<400> 91

```
tttttttttt ttttttttta tgattattat tttttttatt gatctttaca tcctcagtgt 60
tggcagagtt tctgatgctt aataaacatt tgttctgac agataagtgg aaaaaattgt 120
catttcctta ttcaagccat gcttttctgt gatattctga tcctagttag acatacagaa 180
ataaatgtct aaaaacagcac ctcgattctc gtctataaca ggactaagtt cactgtgac 240
ttaaataagc ttggctaaaa tgggacatga gtggaggtag tcacacttca ggaagaaag 300
agaatctcct gtataatctc accaggagat tcaacgaatt ccaccacact ggactagtgg 360
atccccggg ctgcaggaat tcgatatcaa gcttatcgat accgtcgacc tcgagggggg 420
gcccgggtacc caattcgccc tatagttagt cgtattacgc gcgctcactg gccgtcgttt 480
tacaacgtcg tgactgggaa aaccctggcg ttacccaact taatcgctt gcagcacatc 540
cccctttcgc cagctggcgt aatagcgaan agcccgacc gatcgccctt ncaacagttg 600
cgcagcctga atggcgaatg ggacgcgccc ttagcgggcg cattaaagcg cggcnggggtg 660
tggnggntcc cccacgtgac cgnacactt ggcagcgct tacgcccgtc nttcgctttc 720
ttcccttctt ttctgcacc gttcgccggg ttcccccgn agctnttaat cgggggnctc 780
cctttanggg tncnaattaa nggnttacng gaccttngan cccaaaaact ttgattaggg 840
ggaaggtccc cgaagggg 858
```

<210> 92

<211> 585

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 317, 319, 320, 321, 325, 327, 328, 330, 331, 332, 460, 462, 483, 485, 487, 523, 538, 566, 584

<223> n = A,T,C or G

<400> 92
gttgaatctc ctggtgagat tatacaggag attctctttc ttcgctgaag tgtgactacc 60
tccactcatg tcccatttta gccaaagctta ttttaagatca cagtgaactt agtcctgtta 120
tagacgagaa tcgaggtgct gtttttagaca tttattttctg tatgttcaac taggatcaga 180
atatcacaga aaagcatggc ttgaataagg aaatgacaat tttttccact tatctgatca 240
gaacaaatgt ttattaagca tcagaaactc tgccaacact gaggatgtaa agatcaataa 300
aaaaaataat aatcatnann naaanannan nngaaggcg gccgccaccg cgggtggagct 360
ccagcttttg ttcccttttag tgaggggttaa ttgcgcgctt ggcgttaatc atggtcatag 420
ctgttttctg tgtgaaattg ttatccggct cacaattccn cncaacatac gagccgggaa 480
gcntnangtg taaaagcctg ggggtgccta attgagttag ctnactcaca ttaattgngt 540
tgcgctccac ttgcccgctt ttccantccg ggaaacctgt tcgnc 585

<210> 93
<211> 567
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 82, 158, 230, 232, 253, 266, 267, 268, 269, 270, 271, 272,
273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284,
285, 286, 287, 295, 303, 307, 314, 349, 352, 354, 356, 366,
369, 379, 382, 386, 393, 404, 427, 428, 446, 450, 452
<223> n = A,T,C or G

<221> misc_feature
<222> 453, 454, 459, 462, 480, 481, 483, 488, 493, 501, 509, 511,
512, 518, 520, 525, 526, 532, 541, 557
<223> n = A,T,C or G

<400> 93
cggcagtgtt gctgtctgcy tgtccacctt ggaatctggc tgaactggct gggaggacca 60
agactcgggc tggggtgggc anggaaggga accgggggct gctgtgaagg atcttggaac 120
ttccctgtac ccaccttccc cttgcttcat gtttgtnag gaaccttgtg ccggccaagc 180
ccagtttctt tgtgtgatac actaatgtat ttgctttttt tgggaaatan anaaaaatca 240
attaaattgc tantgtttct ttgaannnnn nnnnnnnnnn nnnnnnnngg gggngcgccc 300
ccnccgngga aacnccccct tttgttccct ttaattgaaa ggtaaatng cncnctggc 360
gttaancntt gggccaaanc tngttncccg tngtgaatt gttnatcccc tcccaaattc 420
ccccccnnc ttccaaaccc ggaaancctn annntgttna ancccggggg gttgcctaan 480
ngnaattnaa ccnaaccccc nttaaatng nntttgcncn ccacnngccc cncctttcca 540
nttcggggaa aacctntcc gtgccca 567

<210> 94
<211> 620
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 169, 171, 222, 472, 528, 559, 599
<223> n = A,T,C or G

<400> 94
actagtcaaa aatgctaaaa taatttgga gaaaatattt ttaagttagt gttatagttt 60
catgtttatc ttttattatg ttttgtgaag ttgtgtcttt tcactaatta cctatactat 120
gccaatattt ctttatatct atccataaca tttatactac atttgtaana naatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca anatttaata atctgatcaa 240

```

gttcttgtta tttccaaata gaatggactt ggtctgttaa gggctaagga gaagaggaag 300
ataaggttaa aagttgttaa tgaccaaaca ttctaaaaga aatgcaaaaa aaaagtttat 360
tttcaagcct tcgaactatt taaggaaagc aaaatcattt cctaaatgca tatcatttgt 420
gagaatttct cattaatatc ctgaatcatt catttcacta aggctcatgt tnactccgat 480
atgtctctaa gaaagtacta tttcatggtc caaacctggt tgccatantt gggtaaaggc 540
tttccottaa gtgtgaaant atttaaaatg aaattttcct ctttttaaaa attctttana 600
aggggttaagg gtgttgggga                                     620

```

<210> 95
 <211> 470
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 61, 67, 79, 89, 106, 213, 271, 281, 330, 354, 387, 432, 448
 <223> n = A,T,C or G

```

<400> 95
ctcgaccttc tctgcacagc ggatgaaccc tgagcagctg aagaccagaa aagccactat 60
nactttntgc ttaattcang agcttacang attcttcaaa gagtgngtcc agcatccttt 120
gaaacatgag ttcttaccag cagaagcaga cctttacccc accacctcag cttcaacagc 180
agcagggtgaa acaaccatc cagcctccac ctnaggaaat atttgttccc acaaccaagg 240
agccatgcca ctcaaagggt ccacaacctg naaacacaaa nattccagag ccaggctgta 300
ccaagggtccc tgagccaggg ctgtaccaan gtccctgagc cagggtgtac caangtcctt 360
gagccaggat gtaccaaggt ccctgancca ggttgtccaa ggtccctgag ccaggctaca 420
ccaagggcct gngccaggca gcatcaangt ccctgaccaa ggcttatcaa 470

```

<210> 96
 <211> 660
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 299, 311, 360, 426, 538, 540, 542, 553, 563, 565, 592, 603,
 604, 618, 633, 647, 649, 651, 653
 <223> n = A,T,C or G

```

<400> 96
tttttttttt tttttttttt ggaattaaaa gcaatttaat gagggcagag caggaaacat 60
gcattttctt tcattcgaat cttcagatga accctgagca gccgaagacc agaaaagcca 120
tgaagacttt ctgcttaatt caggggctta caggattctt cagagtgtgt gtgaacaaaa 180
gctttatagt acgtattttt aggatacaaa taagagagag actatggctt ggggtgagaa 240
tgtactgatt acaagggtcta cagacaatta agacacagaa acagatggga agagggtgnc 300
cagcatctgg nggttggtt ctcaagggtt tgtctgtgca ccaaattact tctgcttggc 360
cttctgctga gctgggcttg gagtgaccgt tgaaggacat ggctctggta cctttgtgta 420
gcctgncaca ggaacttttg tgtatccttg ctcaggaact ttgatggcac ctggctcagg 480
aaacttgatg aagccttggt caaggacct tgatgcttgc tggctcaggg accttggnn 540
ancctgggct caggacctt tgnncnaacc ttggcttcaa gggacccttg gnacatcctg 600
gcnnagggac ccttggnncc aaccctgggc ttnagggacc ctttggnntnc nanccttggc 660

```

<210> 97
 <211> 441
 <212> DNA
 <213> Homo sapiens

<220>
<221> misc_feature
<222> 12, 308
<223> n = A,T,C or G

<400> 97
gggaccatac anagtattcc tctcttcaca ccaggaccag ccactgttgc agcatgagtt 60
cccagcagca gaagcagccc tgcattccac cccctcagct tcagcagcag caggtgaaac 120
agccttgcca gcctccacct caggaaacct gcattcccaa aaccaaggag ccctgccacc 180
ccaagggtgc tgagccctgc caccocaaag tgccctgagcc ctgccagccc aaggttccag 240
agccatgcca cccaagggtg cctgagccct gcccttcaat agtactcca gcaccagccc 300
agcagaanac caagcagaag taatgtggtc cacagccatg cccttgagga gccggccacc 360
agatgctgaa tcccctatcc cattctgtgt atgagtccca ttgctcttgc aattagcatt 420
ctgtctcccc caaaaaaaaaa a 441

<210> 98
<211> 600
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 295, 349, 489, 496, 583
<223> n = A,T,C or G

<400> 98
gtattcctct cttcacacca ggaccagcca ctgttgcagc atgagttccc agcagcagaa 60
gcagccctgc atcccacccc ctcagcttca gcagcagcag gtgaaacagc cttgccagcc 120
tccacctcag gaaccatgca tccccaaaac caaggagccc tgccacccca aggtgcctga 180
gccctgccac cccaaagtgc ctgagccctg ccagcccaag gtccagagc catgccaccc 240
caagggtgct gagccctgcc cttcaatagt cactccagca ccagcccagc agaanaccaa 300
gcagaagtaa tgggtccac agccatgccc ttgaggagcc gccaccana tgctgaatcc 360
cctatcccat tctgtgtatg agtccattt gcccttgaat tagcattctg tctcccccac 420
aaaagaatgt gctatgaagc tttctttcct acacactctg agtctctgaa tgaagctgaa 480
ggtcttaant acagancatg ttttcagctg ctgagaattc tctgaagaaa agattttaaga 540
tgaaaggcaa atgattcagc tccttattac cccattaaat tcnctttcaa ttccaaaaaa 600

<210> 99
<211> 667
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 345, 562, 635
<223> n = A,T,C or G

<400> 99
actagtgact gagttcctgg caaagaaatt tgacctggac cagttgataa ctcattgttt 60
accatttaaa aaaatcagtg aaggatttga gctgctcaat tcaggacaaa gcattcgaac 120
ggtcctgacg ttttgagatc caaagtggca ggaggtctgt gttgtcatgg tgaactggag 180
tttctcttgt gagagttccc tcatctgaaa tcatgtatct gtctcacaaa tacaagcata 240
agtagaagat ttgttgaaga catagaaccc ttataaagaa ttattaacct ttataaacat 300
ttaaagtctt gtgagcacct gggaattagt ataataacaa tgttnatatt tttgatttac 360
atthttgtaag gctataattg tatcttttaa gaaaacatac cttggatttc tatgttgaaa 420
tgagagattt taagagttt aaccagctgc tgcagatata ttactcaaaa cagatatagc 480
gtataaagat atagtaaatg catctcctag agtaatatcc acttaacaca ttggaaacta 540

ttatttttta gatttgaata tnaatgttat tttttaaaca cttgttatga gttacttggg 600
attacatttt gaaatcagtt cattccatga tgcanattac tgggattaga ttaagaaaga 660
cggaataa 667

<210> 100

<211> 583

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 404, 506, 514, 527, 528, 538, 548, 556, 568, 569

<223> n = A,T,C or G

<400> 100

gttttgtttg taagatgatc acagtcatgt tacactgatc taaaggacat atatataacc 60
ctttaaaaaa aaaatcactg cctcattctt atttcaagat gaatttctat acagactaga 120
tgtttttctg aagatcaatt agacattttg aaaatgattt aaagtgtttt ccttaatgtt 180
ctctgaaaac aagtttcttt tgtagtttta accaaaaaag tgcccttttt gtcactggat 240
tctcctagca ttcattgattt ttttttcata caatgaaatt aaaattgcta aaatcatgga 300
ctggctttct ggttggattt caggtaagat gtgtttaagg ccagagcttt tctcagtatt 360
tgattttttt ccccaatatt tgatttttta aaaatataca catnggtgct gcatttatat 420
ctgctggttt aaaattctgt catatttcac ttctagcctt ttagttatgg caaatcatat 480
tttactttta cttaaagcat ttggnattt ggantatctg gttctannct aaaaaaanta 540
attctatnaa ttgaantttt ggtactcnnn catatttgga tcc 583

<210> 101

<211> 592

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 218, 497, 502, 533, 544, 546, 548, 550, 555

<223> n = A,T,C or G

<400> 101

gtggagacgt acaaagagca gccgctcaag acacctggga agaaaaagaa aggcaagccc 60
gggaaacgca aggagcagga aaagaaaaaa cggcgaactc gctctgcctg gttagactct 120
ggagtgcactg ggagtgggct agaaggggac cacctgtctg acacctccac aacgtcgtcg 180
gagctcgatt cacggaggca ttgaaatttt cagcaganac cttccaagga catattgcag 240
gattctgtaa tagtgaacat atggaaagta ttagaaatat ttattgtctg taaatactgt 300
aaatgcattg gaataaaact gtctccccc aaggctaatc aaactgcaca ttggtcattg 360
tgaatatttt tttttttgcc aaggctaato caattattat tatcacattt accataattt 420
attttgtcca ttgatgtatt tattttgtaa atgtatcttg gtgctgctga atttctatat 480
tttttgtaca taatgcnttt anatatacct atcaagtttg ttgataaatg acncaatgaa 540
gtgncncnan ttgngggttg aatttaatga atgcctaatt ttattatccc aa 592

<210> 102

<211> 587

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 91, 131, 256, 263, 332, 392, 400, 403, 461, 496, 497, 499,
510, 511, 518, 519, 539, 554, 560, 576

<223> n = A,T,C or G

<400> 102
 cgtcctaagc acttagacta catcagggaa gaacacagac cacatccctg toctcatgcg 60
 gcttatgttt tctggaagaa agtggagacc nagtccttgg ctttagggct ccccggtcg 120
 gggctgtgca ntccgggtcag ggcggaagg gaaatgcacc gctgcatgtg aacttacagc 180
 ccaggcggat gcccttccc ttagcactac ctggcctcct gcatccctc gcctcatgtt 240
 cctccacct tcaanaatg aanaacccca tgggccagc cccttgccct ggggaaccaa 300
 ggcagccttc caaaactcag gggctgaagc anactattag ggcaggggct gactttgggt 360
 gacactgccc attccctctc agggcagctc angtcaccn ggnctcttga acccagcctg 420
 ttcccttgaa aaagggaaca actgaaaagg gcttttcta naaaaagaaa aaccaggga 480
 ctttgccagg gcttcnntnt taccaaaacn ncttctcnng gatttttaat tccccattng 540
 gcctccactt accnggggcn atgccccaaa attaanaatt tcccatc 587

<210> 103
 <211> 496
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 2, 17, 66, 74, 82, 119, 164, 166, 172, 200, 203, 228, 232,
 271, 273, 415, 423, 445, 446, 473
 <223> n = A,T,C or G

<400> 103
 anaggactgg ccctacntgc tctctctcgt cctacctatc aatgccaac atggcagaac 60
 ctgcanccct tggncactgc anatggaaac ctctcagtgt cttgacatca ccctaccnt 120
 gcgggtgggtc tccaccacaa ccactttgac tctgtgttcc ctgnanggtg gnttctcctg 180
 actggcagga tggaccttan ccnacatata cctctgttcc ctctgctnag anaaagaatt 240
 cccttaacat gatataatcc acccatgcaa ntngctactg gccagctac catttaccat 300
 ttgcctacag aatttcattc agtctacact ttggcattct ctctggcgat agagtgtggc 360
 tgggctgacc gcaaaagggtg ccttacacac tggcccccac cctcaaccgt tgacncaatca 420
 gangcttgcc tctccttct gattnncccc catgttggat atcagggtgc tcnagggatt 480
 ggaaaagaaa caaaac 496

<210> 104
 <211> 575
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 18, 19, 45, 68, 77, 132, 155, 174, 219, 226, 238, 259, 263,
 271, 273, 306, 323, 339, 363, 368, 370, 378, 381, 382, 436,
 440, 449, 450, 456, 481, 485, 496, 503, 510, 512, 515, 528,
 542, 552
 <223> n = A,T,C or G

<400> 104
 gcacctgctc tcaatccnnc tctcaccatg atcctccgcc tgcanaaact cctctgcca 60
 ctatggangt ggtttcnngg gtggctcttg ccaactggga agaagccgtg gtgtctctac 120
 ctgttcaact cngtttgtgt ctgggggac aactnngggc tatggaagcg gctnaactgt 180
 tgttttggtg gaagggcttg taattggcct tgggaagtng cttatngaag ttggcctnng 240
 gaagttgcta ttgaaagtng ccttggaagt ngntttgggt ggggttttg ctggtggcct 300
 ttgttnaatt tgggtgcttt gtnaatggcg gccccctcnc ctgggcaatg aaaaaaatca 360
 ccnatgcngn aaacctcnac nnaacagcct gggcttccct cacctcgaaa aaagttgctc 420
 ccccccaaaa aaaggncaan cccctcaann tggaangttg aaaaaatcct cgaatgggga 480
 nccnnaaaac aaaaancccc ccttttccn gnaangggg aaataccncc cccccactta 540

cnaaaaccct tntaaaaaac cccccgggaa aaaaa

575

<210> 105

<211> 619

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 260, 527, 560, 564, 566, 585, 599

<223> n = A,T,C or G

<400> 105

cactagtagg atagaaacac tgtgtcccgga gagtaaggag agaagctact attgattaga 60
gcctaaccoca gggttaactgc aagaagaggc gggataacttt cagctttcca tgtaactgta 120
tgcataaagc caatgtagtc cagtttctaa gatcatgttc caagctaact gaatcccaact 180
tcaatacaca ctcatgaact cctgatggaa caataacagg cccaagcctg tggatatgatg 240
tgcacacttg ctgactcan aaaaaatact actctcataa atgggtggga gtattttggt 300
gacaacctac tttgcttggc tgagtgaagg aatgatattc atatattcat ttattccatg 360
gacatttagt tagtgctttt tatataccag gcatgatgct gagtgacact cttgtgtata 420
tttccaaatt tttgtacagt cgctgcacat atttgaaatc atatattaag acttccaaaa 480
aatgaagtcc ctggtttttc atggcaactt gatcagtaaa ggattcncct ctggttggtgta 540
cttaaaacat ctactatatn gttanatga aattcctttt ccccnctcc cgaaaaana 600
aagtgggtggg gaaaaaaa 619

<210> 106

<211> 506

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 8, 21, 31, 32, 58, 75, 89, 96, 99, 103, 122, 126, 147, 150,
158, 195, 210, 212, 219, 226, 246, 248, 249, 255, 258, 261,
263, 265, 275, 304, 317, 321, 331, 337, 340, 358, 371, 377,
380, 396, 450, 491

<223> n = A,T,C or G

<400> 106

cattggttct ttcatttgct ntggaagtgt nnatctctaa cagtggacaa agttcccngt 60
gccttaaact ctgtnacact tttgggaant gaaaanttng tantatgata ggttattctg 120
angtanagat gttctggata ccattanatn tgcccccngt gtcagaggct catatttgtt 180
tatgtaaatg gtaatncatt cgctactatn antcaattng aaatanggtc tttgggttat 240
gaatantnng cagcncanct nanangctgt ctgtngtatt cattgtggtc atagcacctc 300
acancattgt aacctcnatc nagtgagaca nactagnaan ttcctagtga tggctcanga 360
ttccaaatgg nctcatntcn aatgtttaa agttanttaa gtgtaagaaa tacagactgg 420
atgttccacc aactagtacc tgtaatgaacn ggcctgtccc aacacatctc ccttttccat 480
gactgtggtgta ncccgcatcg gaaaaa 506

<210> 107

<211> 452

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 289, 317, 378

<223> n = A,T,C or G

<400> 107
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tggaagtaa ctgtganaac ccagtttccc gtccatctcc cttagggaact acccatagaa 360
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<210> 108

<211> 502

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 22, 31, 126, 168, 183, 205, 219, 231, 236, 259, 283, 295,
296, 298, 301, 340, 354, 378, 383, 409, 433, 446, 455, 466,
488

<223> n = A,T,C or G

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<210> 109

<211> 1308

<212> DNA

<213> Homo sapiens

<400> 109

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<210> 110

<211> 391

<212> PRT

<213> Homo sapiens

<400> 110

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Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala
35     40     45
Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
50     55     60
Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Ile Glu Asn Thr Glu
65     70     75     80
Ala Val His Gln Gln Phe Gln Lys Phe Leu Thr Glu Ile Ser Lys Leu
85     90     95
Thr Asn Asp Tyr Glu Leu Asn Ile Thr Asn Arg Leu Phe Gly Glu Lys
100    105    110
Thr Tyr Leu Phe Leu Gln Lys Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr
115    120    125
His Ala Ser Leu Glu Pro Val Asp Phe Val Asn Ala Ala Asp Glu Ser
130    135    140
Arg Lys Lys Ile Asn Ser Trp Val Glu Ser Lys Thr Asn Glu Lys Ile
145    150    155    160
Lys Asp Leu Phe Pro Asp Gly Ser Ile Ser Ser Ser Thr Lys Leu Val
165    170    175
Leu Val Asn Met Val Tyr Phe Lys Gly Gln Trp Asp Arg Glu Phe Lys
180    185    190
Lys Glu Asn Thr Lys Glu Glu Lys Phe Trp Met Asn Lys Ser Thr Ser
195    200    205
Lys Ser Val Gln Met Met Thr Gln Ser His Ser Phe Ser Phe Thr Phe
210    215    220
Leu Glu Asp Leu Gln Ala Lys Ile Leu Gly Ile Pro Tyr Lys Asn Asn
225    230    235    240
Asp Leu Ser Met Phe Val Leu Leu Pro Asn Asp Ile Asp Gly Leu Glu
245    250    255
Lys Ile Ile Asp Lys Ile Ser Pro Glu Lys Leu Val Glu Trp Thr Ser
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Pro Gly His Met Glu Glu Arg Lys Val Asn Leu His Leu Pro Arg Phe
275    280    285
Glu Val Glu Asp Ser Tyr Asp Leu Glu Ala Val Leu Ala Ala Met Gly
290    295    300
Met Gly Asp Ala Phe Ser Glu His Lys Ala Asp Tyr Ser Gly Met Ser
305    310    315    320
Ser Gly Ser Gly Leu Tyr Ala Gln Lys Phe Leu His Ser Ser Phe Val
325    330    335
Ala Val Thr Glu Glu Gly Thr Glu Ala Ala Ala Ala Thr Gly Ile Gly
340    345    350
Phe Thr Val Thr Ser Ala Pro Gly His Glu Asn Val His Cys Asn His
355    360    365
Pro Phe Leu Phe Phe Ile Arg His Asn Glu Ser Asn Ser Ile Leu Phe

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370 375 380
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 385 390

<210> 111
 <211> 1419
 <212> DNA
 <213> Homo sapiens

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 ggcgcgcgtca gcactcgact tgggtttgat cttttcaaag agctgaagaa aacaaatgat 180
 ggcaacatct tcttttcccc tgtgggcata ttgactgcaa ttggcatggt cctcctgggg 240
 acccgaggag ccaccgcttc ccagttggag gaggtgtttc actctgaaaa agagacgaag 300
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 attgagaaca cagaagcagt acatcaacaa ttccaaaagt ttttgactga aataagcaaa 420
 ctactaatg attatgaact gaacataacc aacaggctgt ttggagaaaa aacatacctc 480
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<210> 112
 <211> 400
 <212> PRT
 <213> Homo sapiens

<400> 112
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 35 40 45
 Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys
 50 55 60
 Ser Ser Arg Ile Lys Ala Glu Glu Lys Glu Val Val Arg Ile Lys Ala
 65 70 75 80
 Glu Gly Lys Glu Ile Glu Asn Thr Glu Ala Val His Gln Gln Phe Gln
 85 90 95
 Lys Phe Leu Thr Glu Ile Ser Lys Leu Thr Asn Asp Tyr Glu Leu Asn
 100 105 110
 Ile Thr Asn Arg Leu Phe Gly Glu Lys Thr Tyr Leu Phe Leu Gln Lys
 115 120 125

Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr His Ala Ser Leu Glu Pro Val
 130 135 140
 Asp Phe Val Asn Ala Ala Asp Glu Ser Arg Lys Lys Ile Asn Ser Trp
 145 150 155 160
 Val Glu Ser Lys Thr Asn Glu Lys Ile Lys Asp Leu Phe Pro Asp Gly
 165 170 175
 Ser Ile Ser Ser Ser Thr Lys Leu Val Leu Val Asn Met Val Tyr Phe
 180 185 190
 Lys Gly Gln Trp Asp Arg Glu Phe Lys Lys Glu Asn Thr Lys Glu Glu
 195 200 205
 Lys Phe Trp Met Asn Lys Ser Thr Ser Lys Ser Val Gln Met Met Thr
 210 215 220
 Gln Ser His Ser Phe Ser Phe Thr Phe Leu Glu Asp Leu Gln Ala Lys
 225 230 235 240
 Ile Leu Gly Ile Pro Tyr Lys Asn Asn Asp Leu Ser Met Phe Val Leu
 245 250 255
 Leu Pro Asn Asp Ile Asp Gly Leu Glu Lys Ile Ile Asp Lys Ile Ser
 260 265 270
 Pro Glu Lys Leu Val Glu Trp Thr Ser Pro Gly His Met Glu Glu Arg
 275 280 285
 Lys Val Asn Leu His Leu Pro Arg Phe Glu Val Glu Asp Ser Tyr Asp
 290 295 300
 Leu Glu Ala Val Leu Ala Ala Met Gly Met Gly Asp Ala Phe Ser Glu
 305 310 315 320
 His Lys Ala Asp Tyr Ser Gly Met Ser Ser Gly Ser Gly Leu Tyr Ala
 325 330 335
 Gln Lys Phe Leu His Ser Ser Phe Val Ala Val Thr Glu Glu Gly Thr
 340 345 350
 Glu Ala Ala Ala Ala Thr Gly Ile Gly Phe Thr Val Thr Ser Ala Pro
 355 360 365
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<210> 113

<211> 957

<212> DNA

<213> Homo sapiens

<400> 113

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 <211> 161
 <212> PRT
 <213> Homo sapiens

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 Phe Val Pro Thr Thr Lys Glu Pro Cys His Ser Lys Val Pro Gln Pro
 35 40 45
 Gly Asn Thr Lys Ile Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
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 Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
 65 70 75 80
 Gly Cys Thr Lys Val Pro Glu Pro Gly Cys Thr Lys Val Pro Glu Pro
 85 90 95
 Gly Tyr Thr Lys Val Pro Glu Pro Gly Ser Ile Lys Val Pro Asp Gln
 100 105 110
 Gly Phe Ile Lys Phe Pro Glu Pro Gly Ala Ile Lys Val Pro Glu Gln
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 Cys Pro Ser Thr Val Thr Pro Gly Pro Ala Gln Gln Lys Thr Lys Gln
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 Lys

<210> 115
 <211> 506
 <212> DNA
 <213> Homo sapiens

<220>
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 158, 195, 210, 212, 219, 226, 246, 248, 249, 255, 258, 261,
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 380, 396, 450, 491
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<210> 116
 <211> 3079
 <212> DNA

<213> Homo sapiens

<400> 116

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<210> 117

<211> 6921

<212> DNA

<213> Homo sapiens

<400> 117

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<210> 120

<211> 587

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 91, 131, 256, 263, 332, 392, 400, 403, 461, 496, 497, 499, 510, 511, 518, 519, 539, 554, 560, 576

<223> n = A,T,C or G

<400> 120

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<210> 121

<211> 619

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 260, 527, 560, 564, 566, 585, 599

<223> n = A,T,C or G

<400> 121

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<210> 122

<211> 1475

<212> DNA

<213> Homo sapiens

<400> 122

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<210> 123

<211> 2294

<212> DNA

<213> Homo sapiens

<400> 123

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<210> 124

<211> 956

<212> DNA

<213> Homo sapiens

<400> 124

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<211> 486

<212> DNA

<213> Homo sapiens

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<221> misc_feature

<222> 16

<223> n = A,T,C or G

<400> 125

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<210> 126

<211> 3552

<212> DNA

<213> Homo sapiens

<400> 126

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<210> 127

<211> 754

<212> DNA

<213> Homo sapiens

<400> 127

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<210> 128

<211> 374

<212> DNA

<213> Homo sapiens

<400> 128

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<210> 129

<211> 546

<212> DNA

<213> Homo sapiens

<400> 129

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<210> 130

<211> 5156

<212> DNA

<213> Homo sapiens

<400> 130

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<210> 131

<211> 671

<212> DNA

<213> Homo sapiens

<400> 131

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<210> 132

<211> 590

<212> DNA

<213> Homo sapiens

<400> 132

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<210> 133

<211> 581

<212> DNA

<213> Homo sapiens

<400> 133

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<210> 134

<211> 4797

<212> DNA

<213> Homo sapiens

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<222> 135, 501, 4421, 4467, 4468, 4698

<223> n = A,T,C or G

<400> 134

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<210> 135

<211> 2856

<212> DNA

<213> Homo sapiens

<400> 135

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```

<210> 136

<211> 356

<212> DNA

<213> Homo sapiens

<400> 136

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aggcattgat gatgatgaag attttatctc cagcaccatt tcaaccacac caggggcttt 120
tgaccacaca aaacagaacc aggactggac tcagtggaa ccaagccatt caaatccgga 180
agtgtacttt cagacaacca caaggatgac tgatgtagac agaaatggca ccactgttta 240
tgaaggaaac tggaacccag aagcacacc tccctcatt caccatgagc atcatgagga 300
agaagagacc ccacattcta caagcacaat ccaggcaact cctagtagta caacgg 356

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<210> 137

<211> 356

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 254, 264, 279, 281, 290, 328, 342

<223> n = A,T,C or G

<400> 137

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cgctaaggcc aaanttocag acanayggcc gggccggtn nataggggan cccaacttgg 300
ggacccaaac tctggcgcgg aaacacang gcataagctt gnttctctgt gggaaa 356

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<210> 138

<211> 353

<212> DNA

<213> Homo sapiens

<400> 138

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aggtccagtc ctccacttgg cctgatgaga gtggggagtg gcaagggagc tttctcctgc 60
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tacattgatg tggaaattgc tgctgtacc accacctcct gaagaggctt ccctgatgcc 180
aatgccagcc atcttggcat cctggccctc gagcaggctg cggttaagtag cgtatctcctg 240
ctccagccgt gtctttatgt caagcagcat cttgtactcc tggttctgag cctccatctc 300

```

gcacgcggagc tcactcagac ctgcscgsg mssmcgctam gccgaattcc agc 353

<210> 139

<211> 371

<212> DNA

<213> Homo sapiens

<400> 139

agcgtggtcg cggccgaggt ccatccgaag caagattgca gatggcagtg tgaagagaga 60
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 agccttggaa aggtcactga aaaatcttca attggattat gttgacctct accttattca 180
 ttttccagtg tctgtaaagc caggtgagga agtgatccca aaagatgaaa atggaaaaat 240
 actatttgac acagtggatc tctgtgccac gtgggaggcc gtggagaagt gtaaagatgc 300
 aggattggac ctgcccgggc ggccgctcga aagccgaatt ccagcacact ggcggccggt 360
 actagtggat c 371

<210> 140

<211> 370

<212> DNA

<213> Homo sapiens

<400> 140

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 aatagaggta tttttaggct atttttgtaa tatggcttct ggtcaaaatc cctgtgtagc 240
 tgaattccca agccctgcat tgtacagccc cccactcccc tcaccaccta ataaaggaat 300
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 gcacactggc 370

<210> 141

<211> 371

<212> DNA

<213> Homo sapiens

<400> 141

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 aaggagcttc aggttcctgg tactcctcca cagaatactc ggagtattca gactactcat 180
 catcctcagg ggttaccgcg tcttctcct ctgcatgaga gacgcggagc acaggcacag 240
 catggagctg ggagccggca gtgtctgcag cataactagg gaggggtcgt gatccagatg 300
 cgatgaactg gccctggcag gcacagtgtc gactcatctc ttggcgacct gcccgggcgg 360
 ccgctcgaag c 371

<210> 142

<211> 343

<212> DNA

<213> Homo sapiens

<400> 142

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 agagcagttt tgaacactc tttttagaa tttgcaagcg gatgattgga tcgctatgag 180
 gtcttcattg gaaacgggat acctttacat aaaaactaga cagtagcatt ctcagaaatt 240
 tctttgggat gtgggcattc aaccacaga ggagaacttc atttgataga gcagttttga 300
 aacacccttt ttgtagaatc tacagggtga catttagagt gct 343

<210> 143

<211> 354
<212> DNA
<213> Homo sapiens

<400> 143
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gtggtggagt gtgtcatgaa caatgtcacc tgtactcgga tctatgaaaa agtagaataa 180
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agcaaatttc catactgttt ctttcttttt tttttcatta ctgtgttcaa ttatctttat 300
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<210> 144
<211> 353
<212> DNA
<213> Homo sapiens

<400> 144
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aggtttgctt gataccagac ctgtggcccc acctcccatg caggtctctg tgg 353

<210> 145
<211> 371
<212> DNA
<213> Homo sapiens

<400> 145
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ttcctgagac ttgtggcct ctccgttgag tccacttggc tttctgtcct ccacagctcc 120
attgccactg ttgatcacta gctttttctt ctgcccacac cttcttcgac tgttgactgc 180
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tggaatttgg ggtgtcctta taggaccaga ggttgtgttt gctccacctt cttgactccc 300
atgtgagacc tcggccgcga ccacgctaag ccgaattcca gcacactggc ggcccgttac 360
tagtggtatcc g 371

<210> 146
<211> 355
<212> DNA
<213> Homo sapiens

<400> 146
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caggatggcg agtagcagcg gctccaaggc tgaattcatt gtcggaggga aatataaact 120
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tggtcaggaa aaagactaca atgtactagt catggatctt ctgggacctc gctc 355

<210> 147
<211> 355
<212> DNA
<213> Homo sapiens

<400> 147

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tttttcccat aatatgggaa atattttaag tctatcattc cattatgagg ataaactgct 300
acatttggtg tatcttcatt ctttgaaaca caatctatoc ttggcactcc ttcag 355

```

<210> 148

<211> 369

<212> DNA

<213> Homo sapiens

<400> 148

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agggagtgtg ccgagggtct ctgagaagggt ttctctcaca tctagaaaga agcgcttaag 180
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gctgcagcag cctccatcca gcctgaggat gacatcaata cacagaggaa gaagagtcag 300
gaaaagatga gagaagttac agactctcct gggcgacccc gagagcttac cattcctcag 360
acttcttca 369

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<210> 149

<211> 620

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 169, 171, 222, 472, 528, 559, 599

<223> n = A,T,C or G

<400> 149

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catgtttatc ttttattatg ttttgtgaag ttgtgtcttt tcaactaatta cctatactat 120
gccaatattt ccttatatct atccataaca tttatactac atttgtaana naatatgcac 180
gtgaaactta acactttata aggtaaaaat gaggtttcca anatttaata atctgatcaa 240
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tttcccttaa gtgtgaaant atttaaaatg aaattttcct ctttttaaaa attctttana 600
agggttaagg gtgttgggga 620

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<210> 150

<211> 371

<212> DNA

<213> Homo sapiens

<400> 150

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ttacttttat a 371

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<210> 151
<211> 4655
<212> DNA
<213> Homo sapiens

<400> 151
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<210> 152

<211> 586

<212> PRT

<213> Homo sapiens

<400> 152

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Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
1          5          10          15
Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
20          25          30
Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
35          40          45
Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
50          55          60
Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
65          70          75          80
His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
85          90          95
Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
100         105         110
Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
115         120         125
Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
130         135         140
Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
145         150         155         160
Glu Gly Gln Ile Ala Pro Ser Ser His Leu Ile Arg Val Glu Gly Asn
165         170         175
Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
180         185         190
Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val

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195	200	205
Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg		
210	215	220
Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val		
225	230	235
Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg		
245	250	255
Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp		
260	265	270
Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr		
275	280	285
His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp		
290	295	300
Glu Leu Val Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu		
305	310	315
Val Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Leu Gln His		
325	330	335
Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu		
340	345	350
Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser		
355	360	365
Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val		
370	375	380
Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr		
385	390	395
Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met		
405	410	415
Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro		
420	425	430
Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro		
435	440	445
Tyr Pro Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys		
450	455	460
Ser Ser Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr		
465	470	475
Gln Ile Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro		
485	490	495
Glu Gln Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln		
500	505	510
Leu His Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser		
515	520	525
Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val		
530	535	540
Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro		
545	550	555
Arg Asp Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn		
565	570	575
Lys Gln Gln Arg Ile Lys Glu Glu Gly Glu		
580	585	

<210> 153

<211> 2007

<212> DNA

<213> Homo sapiens

<400> 153

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<210> 154

<211> 2148

<212> DNA

<213> Homo sapiens

<400> 154

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tggccagggc aattttggag agcaaaaaat ttgcagttag agcagtgacc agggatgtga 180
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<210> 155

<211> 153

<212> PRT

<213> Homo sapiens

<400> 155

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Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
 1           5           10          15
Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
      20           25           30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly
      35           40           45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
      50           55           60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
      65           70           75           80
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Ile Thr
      85           90           95
Pro Glu Ala Phe Glu Lys Leu Gly Phe Pro Ala Ala Lys Glu Ile Ala
      100          105          110
Asn Met Cys Arg Phe Tyr Glu Met Lys Pro Asp Arg Asp Val Asn Leu
      115          120          125
Thr His Gln Leu Asn Pro Lys Val Lys Ser Phe Ser Gln Phe Ile Ser
      130          135          140
Glu Asn Gln Gly Ala Phe Lys Gly Met
145          150

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<210> 156

<211> 128

<212> PRT

<213> Homo sapiens

<400> 156

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Met Thr Ser Val Arg Val Ala Ala Tyr Phe Glu Asn Phe Leu Ala Ala
 1           5           10          15
Trp Arg Pro Val Lys Ala Ser Asp Gly Asp Tyr Tyr Thr Leu Ala Val
      20           25           30
Pro Met Gly Asp Val Pro Met Asp Gly Ile Ser Val Ala Asp Ile Gly

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35	40	45
Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys		
50	55	60
Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp		
65	70	75
Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Thr Ile		
85	90	95
Cys Ala Ile Asp Asp Gln Lys Thr Val Glu Glu Gly Phe Met Glu Asp		
100	105	110
Val Gly Leu Ser Trp Ser Leu Arg Glu His Asp His Val Ala Gly Ala		
115	120	125

<210> 157
 <211> 424
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> 320, 322
 <223> n = A,T,C or G

<400> 157
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 aattcagtc cactgttat attaccttct ccaggaaccc tccagtgggg aaggctgcga 180
 tattagattt cctgtatgc aaagtttttg ttgaaagctg tgctcagagg aggtgagagg 240
 agaggaagga gaaaactgca tcataacttt acagaattga atctagagtc ttccccgaaa 300
 agcccagaaa cttctctgcn gnatctggct tgtccatctg gtctaagggt gctgcttctt 360
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 tgct 424

<210> 158
 <211> 2099
 <212> DNA
 <213> Homo sapiens

<400> 158
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 ccgcgcagag cccgcgccag ggccgcgggc cgcagagcag ttaaaacgtg caggcaccag 180
 aaggcacttc ctgtcgggtga agaagacctg tctccggtgt cacgggcacg ctgtgttttg 240
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 aatgtggga ttgaccctg ccccaacctt gttgactgct ttatttctag gccaacagag 1140

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cggaacagtg tggaagcaga aggccttttt aactcatccg ttgccaatc attgcaaaca 2040
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<210> 159

<211> 291

<212> PRT

<213> Homo sapiens

<400> 159

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20     25     30
Val Met Ile Leu Val Val Ala Ala Gln Glu Val Trp Gly Asp Glu Gln
35     40     45
Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
50     55     60
Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
65     70     75     80
Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
85     90     95
Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg
100    105    110
Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys Gln Lys Val Arg Ile
115    120    125
Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile
130    135    140
Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly
145    150    155    160
Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn
165    170    175
Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
180    185    190
Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
195    200    205
Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg
210    215    220
Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys
225    230    235    240
Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile
245    250    255
Thr Gly Ser Gln Ala Lys His Phe Lys Val Lys Cys Ser Cys Val Ile
260    265    270
Arg Arg Leu Leu Ser Ser Pro Glu Gly Asn Thr Asn Leu Lys Val Pro

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275
Ser Val Ala
290

280

285

<210> 160
<211> 3951
<212> DNA
<213> Homo sapiens

<400> 160
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atgggatgta atcacagact ctgctgactt tcaccacagc ttcccatga acgggactga 960
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<210> 161

<211> 943

<212> PRT

<213> Homo sapiens

<400> 161

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Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
35     40     45
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
50     55     60
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65     70     75     80
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
85     90     95
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
100    105    110
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
115    120    125
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
130    135    140
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145    150    155    160
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
165    170    175
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
180    185    190
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
195    200    205
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
210    215    220
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
225    230    235    240
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
245    250    255

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Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
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 275 280 285
 Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Thr Phe Ser Leu
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 Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser
 305 310 315 320
 Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu
 325 330 335
 Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala
 340 345 350
 Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn
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 Ser Asn Asp Asp Arg Lys Leu Val Ser Tyr Leu Pro Thr Thr Val
 370 375 380
 Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe
 385 390 395 400
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 Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
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 Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
 450 455 460
 Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
 465 470 475 480
 Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
 485 490 495
 Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
 500 505 510
 Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
 515 520 525
 Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
 530 535 540
 Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
 545 550 555 560
 Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
 565 570 575
 Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr
 580 585 590
 Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu
 595 600 605
 Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile
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 Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val
 625 630 635 640
 Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu
 645 650 655
 Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr
 660 665 670
 Ser Arg Tyr Phe Phe Ser Phe Ala Ala Asn Gly Arg Tyr Ser Leu Lys
 675 680 685
 Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile
 690 695 700
 Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn
 705 710 715 720

Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu
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 Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val
 740 745 750
 Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
 755 760 765
 Ile Ile Asp Leu Glu Ala Val Lys Val Glu Glu Glu Leu Thr Leu Ser
 770 775 780
 Trp Thr Ala Pro Gly Glu Asp Phe Asp Gln Gly Gln Ala Thr Ser Tyr
 785 790 795 800
 Glu Ile Arg Met Ser Lys Ser Leu Gln Asn Ile Gln Asp Asp Phe Asn
 805 810 815
 Asn Ala Ile Leu Val Asn Thr Ser Lys Arg Asn Pro Gln Gln Ala Gly
 820 825 830
 Ile Arg Glu Ile Phe Thr Phe Ser Pro Gln Ile Ser Thr Asn Gly Pro
 835 840 845
 Glu His Gln Pro Asn Gly Glu Thr His Glu Ser His Arg Ile Tyr Val
 850 855 860
 Ala Ile Arg Ala Met Asp Arg Asn Ser Leu Gln Ser Ala Val Ser Asn
 865 870 875 880
 Ile Ala Gln Ala Pro Leu Phe Ile Pro Pro Asn Ser Asp Pro Val Pro
 885 890 895
 Ala Arg Asp Tyr Leu Ile Leu Lys Gly Val Leu Thr Ala Met Gly Leu
 900 905 910
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<210> 162

<211> 498

<212> DNA

<213> Homo sapiens

<400> 162

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 gaccaccccc tgccaggact ccttgccaac aggaactgga ccaggtcctg gagcggatct 240
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 gtgcacaccc cagcggat 498

<210> 163

<211> 1128

<212> DNA

<213> Homo sapiens

<400> 163

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 cctcctgcgg gcgctcgggt gaggggtctca gccgccgcct caaaagagct gtgtctgaac 240
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actccaagcc ctctcccaac acaaagaacc accccgtccg atttggtct gatgatgagg 420
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<210> 164

<211> 1310

<212> DNA

<213> Homo sapiens

<400> 164

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<210> 165

<211> 177

<212> PRT

<213> Homo sapiens

<400> 165

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20          25          30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
35          40          45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
50          55          60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro

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65          70          75          80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
      85          90          95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
      100          105          110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly
      115          120          125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
      130          135          140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145          150          155          160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
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His

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<210> 166
 <211> 177
 <212> PRT
 <213> Homo sapiens

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<400> 166
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Ser Tyr Ala Val Pro Ser Cys Gly Arg Ser Val Glu Gly Leu Ser Arg
      20          25          30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
      35          40          45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
      50          55          60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65          70          75          80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
      85          90          95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
      100          105          110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly
      115          120          125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
      130          135          140
Ser Ala Trp Leu Asp Ser Gly Val Thr Gly Ser Gly Leu Glu Gly Asp
145          150          155          160
His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg Arg
      165          170          175
His

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<210> 167
 <211> 3362
 <212> DNA
 <213> Homo sapiens

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<400> 167
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<210> 168

<211> 2784

<212> DNA

<213> Homo sapiens

<400> 168

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<210> 169

<211> 592

<212> PRT

<213> Homo sapiens

<400> 169

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Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn	20	25	30
Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met	35	40	45
Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val	50	55	60
Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn	65	70	75
Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile	85	90	95
Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln	100	105	110
Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn	115	120	125
Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg	130	135	140
Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu	145	150	155
Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys	165	170	175
Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys	180	185	190
Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu	195	200	205
Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile	210	215	220
Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser	225	230	235
Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu	245	250	255
Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser	260	265	270
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu	275	280	285
Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser	290	295	300
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Ala Ala Glu	305	310	315
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala	325	330	335
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn	340	345	350
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val	355	360	365
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe	370	375	380
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile	385	390	395
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr	405	410	415
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser	420	425	430
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys	435	440	445
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe	450	455	460

465 470 475 480
 Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
 485 490 495
 Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
 500 505 510
 Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
 515 520 525
 Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
 530 535 540
 Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
 545 550 555 560
 Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
 565 570 575
 Tyr Thr Leu Met Cys Phe His His Ala Lys Leu Leu Thr Trp Lys Leu
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<210> 170

<211> 791

<212> PRT

<213> Homo sapiens

<400> 170

Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
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 35 40 45
 Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
 50 55 60
 Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
 65 70 75 80
 Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
 85 90 95
 Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
 100 105 110
 Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
 115 120 125
 Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
 130 135 140
 Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
 145 150 155 160
 Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu
 165 170 175
 Tyr Asn Asn Asp Lys Pro Phe Tyr Ile Asn Gly Gln Asn Gln Ile Lys
 180 185 190
 Val Thr Arg Cys Ser Ser Asp Ile Thr Gly Ile Phe Val Cys Glu Lys
 195 200 205
 Gly Pro Cys Pro Gln Glu Asn Cys Ile Ile Ser Lys Leu Phe Lys Glu
 210 215 220
 Gly Cys Thr Phe Ile Tyr Asn Ser Thr Gln Asn Ala Thr Ala Ser Ile
 225 230 235 240
 Met Phe Met Gln Ser Leu Ser Ser Val Val Glu Phe Cys Asn Ala Ser
 245 250 255
 Thr His Asn Gln Glu Ala Pro Asn Leu Gln Asn Gln Met Cys Ser Leu
 260 265 270
 Arg Ser Ala Trp Asp Val Ile Thr Asp Ser Ala Asp Phe His His Ser

275	280	285
Phe Pro Met Asn Gly Thr Glu Leu Pro Pro Pro Pro Thr Phe Ser Leu		
290	295	300
Val Glu Ala Gly Asp Lys Val Val Cys Leu Val Leu Asp Val Ser Ser		
305	310	315
Lys Met Ala Glu Ala Asp Arg Leu Leu Gln Leu Gln Gln Ala Ala Glu		
	325	330
		335
Phe Tyr Leu Met Gln Ile Val Glu Ile His Thr Phe Val Gly Ile Ala		
	340	345
		350
Ser Phe Asp Ser Lys Gly Glu Ile Arg Ala Gln Leu His Gln Ile Asn		
	355	360
		365
Ser Asn Asp Asp Arg Lys Leu Leu Val Ser Tyr Leu Pro Thr Thr Val		
	370	375
		380
Ser Ala Lys Thr Asp Ile Ser Ile Cys Ser Gly Leu Lys Lys Gly Phe		
385	390	395
		400
Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile		
	405	410
		415
Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr		
	420	425
		430
Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser		
	435	440
		445
Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys		
	450	455
		460
Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe		
465	470	475
		480
Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln		
	485	490
		495
Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn		
	500	505
		510
Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val		
	515	520
		525
Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp		
	530	535
		540
Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg		
545	550	555
		560
Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr		
	565	570
		575
Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr		
	580	585
		590
Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu		
	595	600
		605
Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile		
	610	615
		620
Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val		
625	630	635
		640
Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu		
	645	650
		655
Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr		
	660	665
		670
Ser Arg Tyr Phe Phe Ser Phe Ala Asn Gly Arg Tyr Ser Leu Lys		
	675	680
		685
Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile		
	690	695
		700
Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn		
705	710	715
		720
Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu		
	725	730
		735
Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val		

740 745 750
 Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
 755 760 765
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 Asp Ser Thr Trp Arg Arg Leu
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<210> 171
 <211> 1491
 <212> DNA
 <213> Homo sapiens

<400> 171
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 aagtggctct tgtcctgttg ccctgggagt tctcaaattg ctgcagcagc ctccaccag 240
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 caccatattg attctgcaca tgtttacaat aatgaggagc aggttggact ggccatccga 480
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<210> 172
 <211> 364
 <212> PRT
 <213> Homo sapiens

<400> 172
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 Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp
 35 40 45
 Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His
 50 55 60
 Gly Ala Asn Arg Phe Val Pro Lys Ser Lys Ala Leu Glu Ala Val Lys
 65 70 75 80
 Leu Ala Ile Glu Ala Gly Phe His His Ile Asp Ser Ala His Val Tyr

85															90					95				
Asn	Asn	Glu	Glu	Gln	Val	Gly	Leu	Ala	Ile	Arg	Ser	Lys	Ile	Ala	Asp									
								100									110							
Gly	Ser	Val	Lys	Arg	Glu	Asp	Ile	Phe	Tyr	Thr	Ser	Lys	Leu	Trp	Ser									
								115									125							
Asn	Ser	His	Arg	Pro	Glu	Leu	Val	Arg	Pro	Ala	Leu	Glu	Arg	Ser	Leu									
								130									140							
Lys	Asn	Leu	Gln	Leu	Asp	Tyr	Val	Asp	Leu	Tyr	Leu	Ile	His	Phe	Pro									
145									150									160						
Val	Ser	Val	Lys	Pro	Gly	Glu	Glu	Val	Ile	Pro	Lys	Asp	Glu	Asn	Gly									
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Lys	Ile	Leu	Phe	Asp	Thr	Val	Asp	Leu	Cys	Ala	Thr	Trp	Glu	Ala	Met									
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Glu	Lys	Cys	Lys	Asp	Ala	Gly	Leu	Ala	Lys	Ser	Ile	Gly	Val	Ser	Asn									
								195									205							
Phe	Asn	His	Arg	Leu	Leu	Glu	Met	Ile	Leu	Asn	Lys	Pro	Gly	Leu	Lys									
								210									220							
Tyr	Lys	Pro	Val	Cys	Asn	Gln	Val	Glu	Cys	His	Pro	Tyr	Phe	Asn	Gln									
225									230									240						
Arg	Lys	Leu	Leu	Asp	Phe	Cys	Lys	Ser	Lys	Asp	Ile	Val	Leu	Val	Ala									
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Tyr	Ser	Ala	Leu	Gly	Ser	His	Arg	Glu	Glu	Pro	Trp	Val	Asp	Pro	Asn									
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Ser	Pro	Val	Leu	Leu	Glu	Asp	Pro	Val	Leu	Cys	Ala	Leu	Ala	Lys	Lys									
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His	Lys	Arg	Thr	Pro	Ala	Leu	Ile	Ala	Leu	Arg	Tyr	Gln	Leu	Gln	Arg									
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Gly	Val	Val	Val	Leu	Ala	Lys	Ser	Tyr	Asn	Glu	Gln	Arg	Ile	Arg	Gln									
305									310									320						
Asn	Val	Gln	Val	Phe	Glu	Phe	Gln	Leu	Thr	Ser	Glu	Glu	Met	Lys	Ala									
								325									335							
Ile	Asp	Gly	Leu	Asn	Arg	Asn	Val	Arg	Tyr	Leu	Thr	Leu	Asp	Ile	Phe									
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<210> 173
<211> 1988
<212> DNA
<213> Homo sapiens
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aatgtctaaaa	taatttggga	gaaaataatt	tttaagtagt	gttatagttt	catgtttatc	900	

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cttacataat gaaaaccaat tcattttaaa tatcagatta ttattttgta agttgtggaa 1920
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<210> 174

<211> 238

<212> PRT

<213> Homo sapiens

<400> 174

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 35          40          45
Cys Gly Leu Ala Cys Glu Arg Cys Arg Trp Ile Leu Pro Leu Leu Leu
 50          55          60
Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu Ala Gly Arg Gly Trp
 65          70          75          80
Leu Gln Ser Ser Asp His Gly Gln Thr Ser Ser Leu Trp Trp Lys Cys
 85          90          95
Ser Gln Glu Gly Gly Ser Gly Ser Tyr Glu Glu Gly Cys Gln Ser
100          105          110
Leu Met Glu Tyr Ala Trp Gly Arg Ala Ala Ala Ala Met Leu Phe Cys
115          120          125
Gly Phe Ile Ile Leu Val Ile Cys Phe Ile Leu Ser Phe Phe Ala Leu
130          135          140
Cys Gly Pro Gln Met Leu Val Phe Leu Arg Val Ile Gly Gly Leu Leu
145          150          155          160
Ala Leu Ala Ala Val Phe Gln Ile Ile Ser Leu Val Ile Tyr Pro Val
165          170          175
Lys Tyr Thr Gln Thr Phe Thr Leu His Ala Asn Pro Ala Val Thr Tyr
180          185          190
Ile Tyr Asn Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr Ile Ile Leu
195          200          205
Ile Gly Cys Ala Phe Phe Phe Cys Cys Leu Pro Asn Tyr Glu Asp Asp
210          215          220
Leu Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser Ala
225          230          235

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<210> 175
<211> 4181
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 3347, 3502, 3506, 3520, 3538, 3549, 3646, 3940, 3968, 3974,
4036, 4056, 4062, 4080, 4088, 4115
<223> n = A,T,C or G

<400> 175
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ttactgtggt tgtgtatatt aaaggcgaga agacgagggg aacaaaacca gctggatcca 180
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gcaaggatt cggaacttc agatacgaata tatccgcct catttacagt gggaggtgct 540
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tacttctggc tgggtgacagt aaagctggaa aattaatttc agggtttttt gaggcctttg 2760

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gtggtcgag gagattttgg aacggctggt ttaaattggt tcaggagact tcagtttttt 2940
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ataatgtnc cccaatgcag cttcattttc caganacctt gacgcaggat aaattttttc 4140
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<210> 176

<211> 579

<212> PRT

<213> Homo sapiens

<400> 176

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Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
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Asp Leu Glu Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro
20          25          30
Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser
35          40          45
Trp Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His
50          55          60
Gly Lys Pro Ile Glu Val Glu His Ser Val Pro Lys Arg Gln Arg Ile
65          70          75          80
Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu Val
85          90          95
Leu Asp Ser Leu Leu Val Gln Tyr Gly Val Val Glu Ser Cys Glu Gln
100          105          110
Val Asn Thr Asp Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Ser
115          120          125
Lys Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu
130          135          140
Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro Asp Glu Met Ala Ala
145          150          155          160
Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly Gln
165          170          175
Arg Gly Ser Ser Arg Gln Gly Ser Pro Gly Ser Val Ser Lys Gln Lys
180          185          190
Pro Cys Asp Leu Pro Leu Arg Leu Leu Val Pro Thr Gln Phe Val Gly
195          200          205
Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln

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210	215	220
Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala		
225	230	235
Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala Ala		240
	245	250
Cys Lys Ser Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys		255
	260	265
Phe Thr Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val		270
	275	280
Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu Gln		285
	290	295
Asp Thr Asp Thr Lys Ile Thr Ile Ser Pro Leu Gln Glu Leu Thr Leu		300
305	310	315
Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Asn Val Glu Thr Cys		320
	325	330
Ala Lys Ala Glu Glu Glu Ile Met Lys Lys Ile Arg Glu Ser Tyr Glu		335
	340	345
Asn Asp Ile Ala Ser Met Asn Leu Gln Ala His Leu Ile Pro Gly Leu		350
	355	360
Asn Leu Asn Ala Leu Gly Leu Phe Pro Pro Thr Ser Gly Met Pro Pro		365
370	375	380
Pro Thr Ser Gly Pro Pro Ser Ala Met Thr Pro Pro Tyr Pro Gln Phe		385
	390	395
Glu Gln Ser Glu Thr Glu Thr Val His Gln Phe Ile Pro Ala Leu Ser		400
	405	410
Val Gly Ala Ile Ile Gly Lys Gln Gly Gln His Ile Lys Gln Leu Ser		415
	420	425
Arg Phe Ala Gly Ala Ser Ile Lys Ile Ala Pro Ala Glu Ala Pro Asp		430
	435	440
Ala Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe		445
	450	455
Lys Ala Gln Gly Arg Ile Tyr Gly Lys Ile Lys Glu Glu Asn Phe Val		460
465	470	475
Ser Pro Lys Glu Glu Val Lys Leu Glu Ala His Ile Arg Val Pro Ser		480
	485	490
Phe Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu		495
	500	505
Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr		510
	515	520
Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr		525
530	535	540
Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val		545
	550	555
Lys Gln His Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser		560
	565	570
		575

Arg Arg Lys

<210> 177

<211> 401

<212> DNA

<213> Homo sapiens

<400> 177

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 agatccaaac aaatacacat tctgtgtttt agctcagtgt tttctaaaaa aagaaactgc 120
 cacacagcaa aaaattgttt actttgtgtg acaaaccaaa tcagttctca aaaaatgacc 180

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ggtgcttata aaaagttata aatatcgagt agctctaaaa caaaccacct gaccaagagg 240
gaagtgaagt tgtgcttagt atttacattg gatgccagtt ttgtaatcac tgacttatgt 300
gcaaaactggt gcagaaattc tataaactct ttgctgtttt tgafacctgc tttttgtttc 360
atthttgtttt gttttgtaaa aatgataaaa cttcagaaaa t 401

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<210> 178
<211> 561
<212> DNA
<213> Homo sapiens

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<400> 178
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gcccgcctatg ggacaggggt ctttgccag aatgagtacc tacgctatca ggaggccctg 120
agtgaagctgg ccactgcggt taaagcacga attgggagct ctcagcgaca tcaccagtca 180
gcagccaaag acctaactca gtccctgag gtctcccaa caaccatcca ggtgacatac 240
ctccctcca gtcagaagag taaacgtgcc aagcacttcc ttgaattgaa gagctttaag 300
gataactata acacattgga gactactctg tgacggagct gaaggactct tgccgtagat 360
taagccagtc agttgcaatg tgcaagacag gctgcttgcc gggccgcct cggaacatct 420
ggcccagcag gccagactg tatccatcca agttccggt gtatccagag ttcttagagc 480
ttgtgtctaa agggtaattc cccaaccctt ccttatgagc atttttagaa cattggctaa 540
gactatthtc cccagtagc g 561

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<210> 179
<211> 521
<212> DNA
<213> Homo sapiens

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<400> 179
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gatcgagcaa tggcttcagg acatgggttc tcttctctg tgatcattca agtgcctact 120
gcatgaagac tggcttgctc cagtgtttca acctcaccag ggctgtctct tggccacac 180
ctcgtccct gttagtgcg tatgacagcc cccatcaa atgacctggcc aagtcacggt 240
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aggataagtg ggatctacca attgattctg gcaaaacaat ttctaagatt tttttgcttt 480
atgtgggaaa cagatctaaa tctcatttta tgctgtattt t 521

```

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<210> 180
<211> 417
<212> DNA
<213> Homo sapiens

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```

<400> 180
ggtggaattc gccgaagatg gcggaggtgc aggtcctggt gcttgatggt cgaggccatc 60
tcctgggccc cctggcgcc atcgtggcta aacagggtact gctgggcccg aaggtggtgg 120
tcgtacgctg tgaaggcatc aacatttctg gcaatttcta cagaacaag ttgaagtacc 180
tggttttctt ccgcaagcgg atgaacacca acccttccc aggccctac cacttccggg 240
ccccagccg catcttctgg cggaccgtgc gaggtatgct gcccacaaa accaagcgag 300
gcaggccgc tctggaccgt ctcaaggtgt ttgacggcat cccaccgcc tacgacaaga 360
aaaagcggat ggtggttct gctgccctca aggtcgtgct tctgaagcct acaagaa 417

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<210> 181
<211> 283
<212> DNA
<213> Homo sapiens

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<220>

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<221> misc_feature
<222> 35
<223> n = A,T,C or G

<400> 181
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caagaactca agtgtaactg tgataaaata accctttccca ggtatattgg caggatatgtg 120
tgtaatctca gaatacacag gtgacataga tatgatatga caactggtaa tgggtggattc 180
atttacattg ttacacttc tatgaccagg cottaaggga aggtcagttt tttaaaaaac 240
caagtagtgt cttcctacct atctccagat acatgtcaaa aaa 283

<210> 182
<211> 401
<212> DNA
<213> Homo sapiens

<400> 182
atattcttgc tgcttatgca gctgacattg ttgccctccc taaagcaacc aagtagcctt 60
tatttcccac agtgaaagaa aacgctggcc tatcagttac attacaaaag gcagatttca 120
agaggattga gtaagtagtt ggatggcttt cataaaaaca agaattcaag aagaggattc 180
atgctttaag aaacatttgt tatacattcc tcacaaatta tacctgggat aaaaactatg 240
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gctgcaagtc tgcctatct gaattccag cagaagcact aagaagctcc accctatcac 360
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<210> 183
<211> 366
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 325
<223> n = A,T,C or G

<400> 183
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accatcatgc ttgatgttc cctgtcttt ctctctctg ctctcaagag caaagggtta 120
tttaaggaca aagatgaagt cactgtaaac taatctgtca ttgtttttac cttccttttc 180
tttttcagt cagaaattaa aagtaagtat aaagcaccgt gattgggagt gtttttgctg 240
gtgtcggaat cactggtaaa tgttggtgta gaacaatccc tccccttgca cttgtgaaaa 300
cactttgagc gctttaagag attancctga gaaataatta aatatctttt ctcttcaaaa 360
aaaaaa 366

<210> 184
<211> 370
<212> DNA
<213> Homo sapiens

<400> 184
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tttaataatt gtactgagag aaactgctta cgtacacatt gcagatcaaa tatttgagtg 120
taaaatgtta gtctacatag atgggtgatt gtaactttat tgccattaaa agatttcaaa 180
ttgcattcat gcttctgtgt acacataatg aaaaatgggc aaataatgaa gatctctcct 240
tcagctgtct ctgtttaatt ctgctgtctg ctcttctcta atgctgcgtc cctaattgta 300
cacagtttag tgatatctag gagtataaag ttgtcgccca tcaataaaaa tcacaaagtt 360
ggtttaaaaa 370

<210> 185
<211> 107
<212> DNA
<213> Homo sapiens

<400> 185
ctcatattat tttccttttg agaaattgga aactotttct gttgctatta tattaataaa 60
gttggtgttt attttctggt agtcaccttc cccatttaaa aaaaaaa 107

<210> 186
<211> 309
<212> DNA
<213> Homo sapiens

<400> 186
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gccagtgagt gacagtcagt agggagtgtc tcttcttggg gaggaagaa ggtagagcct 180
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tgcccacgta gtggaggcct ctggcagatc ctgcattcca aggtcactgg actgtacgtt 300
tttatggtt 309

<210> 187
<211> 477
<212> DNA
<213> Homo sapiens

<400> 187
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tgccctgcaa gccaggccat ccctgggcgc cacagacgag ctccgagcca ggtcagggtt 180
cggaggccac aagctcagcc tcaggcccag gcactgattg tggcagaggg gccactacc 240
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atgtcttcag aagcaagtca ggtttcatgt aaccgagtgt cctcttgctg gtccaaaagt 420
agcccagggc tgtagcacag gtttcacagt gattttgtgt tcagccgtga gtcacac 477

<210> 188
<211> 220
<212> DNA
<213> Homo sapiens

<400> 188
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ttaaataagt accctgtgag tatgagataa attagtgaca atcagaacaa gtttcagtat 120
cagatgttca agaggaagtt gctattgcat tgattttaat atttgtacat aaacactgat 180
ttttttgagc attattttgt atttgttgta cttaataacc 220

<210> 189
<211> 417
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> 76, 77
<223> n = A,T,C or G

<400> 189
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ccatcattaa gcatcnnttt caaaattata gccattcatg atttactttt tccagatgac 120
tatcattatt ctagtccttt gaatttgtaa ggggaaaaaa aacaaaaaca aaaacttacg 180
atgcactttt ctccagcaca tcagatttca aattgaaaat taaagacatg ctatggtaat 240
gcacttgcta gtactacaca ctttgtacaa caaaaaacag aggcaagaaa caacggaaag 300
agaaaagcct tcctttgttg gcccttaaac tgagtcaaga tctgaaatgt agagatgatc 360
tctgacgata cctgtatgtt cttattgtgt aaataaaatt gctggtatga aatgaca 417

<210> 190
<211> 497
<212> DNA
<213> Homo sapiens

<400> 190
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aacgcaggag ctgtcattga ctggcccaca gaggagggca aggaagtatg ggattatgtg 120
acgggtccgca aggatgccta catgttcttg ttgctctatt atgccaccaa ctccctgcaag 180
aacttctcag aactgccccct ggtcatgttg cttcagggcg gtccaggcgg ttctagcact 240
ggatttggaa actttgagga aattggggccc cttgacagtg atctcaaacc acggaaaacc 300
acctggctcc aggetgccag tctcctatgt gtggataatc ccgtgggcac tgggttcagt 360
tatgtgaatg gtagtggtgc ctatgccaa gacctggcta tgggtggcttc agacatgatg 420
gttctcctga agaccttctt cagttgccac aaagaattcc agacagttcc attctacatt 480
ttctcagagt cctatgg 497

<210> 191
<211> 175
<212> DNA
<213> Homo sapiens

<400> 191
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ctacttgagt acaaggattt gagcctgtta cattcactgc tgaatttttag gctcctggaa 120
gatacccgac attcaataga gaccacacaa taaatatatg tcaaataaaa aaaaa 175

<210> 192
<211> 526
<212> DNA
<213> Homo sapiens

<400> 192
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aagaacagta ttgctgtaat tccttttctt ttcttctctca ttctctctgc cccttaaaag 120
attgaagaaa gagaaacttg tcaactcata tccacgttat ctagcaaagt acataagaat 180
ctatcactaa gtaatgtatc cttcagaatg tgttggttta ccagtgcacac cccatattca 240
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aattcctctg atcactttga gaaacaaact tttattaaat gtaaggcact tttctatgaa 480
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<210> 193
<211> 553
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature

<222> 290, 300, 411, 441

<223> n = A,T,C or G

<400> 193

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cagtggtagc agttggactg accattgctg ctgcaggatt tgcaggccgt tacgttttgc 180
aagccatgaa gcattatggag cctcaagtaa aacaagtttt tcaaagccta ccaaaatctg 240
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cattaatact aggtgtaagc cctactgcca ataaagggaa aataagagat gctcatcgac 360
gaattatgct tttaaatcat cctgacaaag gaggatctcc ttatatagca nccaaaatca 420
atgaagctaa agatttacta naaggtcaag ctaaaaaatg aagtaaatgt atgatgaatt 480
ttaagtctgt attagtttat gtatatgagt actaagtttt tataataaaa tgcctcagag 540
ctacaatttt aaa 553
```

<210> 194

<211> 320

<212> DNA

<213> Homo sapiens

<400> 194

```
cccttcccaa tccatcagta aagaccccat ctgccttgct catgccgttt cccaacaggg 60
atgtcacttg atatgagaat ctcaaatctc aatgccttat aagcattcct tccgtgtgtcc 120
attaagactc tgataattgt ctcccctcca taggaatttc tcccaggaaa gaaatatatc 180
cccatctccg tttcatatca gaactacogt ccccgatatt cccttcagag agattaaaga 240
ccagaaaaaa gtgagcctct tcatctgcac ctgtaatagt ttcagttcct attttcttcc 300
attgacccat atttatacct 320
```

<210> 195

<211> 320

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 203, 218

<223> n = A,T,C or G

<400> 195

```
aagcatgacc tggggaaatg gtcagacctt gtattgtgtt tttggccttg aaagtagcaa 60
gtgaccagaa tctgccatgg caacaggctt taaaaaagac ccttaaaaag acactgtctc 120
aactgtgggt ttagaccag ccagctctct gtacatttgc tagctttagt ttttctaaga 180
ctgagtaaac ttcttatttt tanaaagggg aggcgtggntt gtaactttcc ttgtacttaa 240
ttgggtaaaa gtcttttcca caaaccacca tctattttgt gaactttgtt agtcatcttt 300
tatttggtaa attatgaact 320
```

<210> 196

<211> 357

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 36

<223> n = A,T,C or G

<400> 196

```
atataaaata atacgaaact ttaaaaagca ttggantgtc agtatgttga atcagtagtt 60
```

tcactttaac tgtaaacaaat ttcttaggac accatttggg ctagtttctg tgtaagtgtg 120
aatactacaa aaacttattt atactgttct tatgtcattt gttatattca tagatttata 180
tgatgatatg acatctggct aaaaagaaat tattgcaaaa ctaaccacta tgtacttttt 240
tataaatact gtatggacaa aaaatggcat tttttatatt aaattgttta gctctggcaa 300
aaaaaaaaa ttttaagagc tgggtactaat aaaggattat tatgactgtt aaaaaaa 357

<210> 197

<211> 565

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 27

<223> n = A,T,C or G

<400> 197

tcagctgagt accatcagga tatttanccc ttttaagtgt gttttgggag tagaaaaacta 60
aagcaacaat acttcctctt gacagctttg attggaatgg ggttattaga tcattcacct 120
tggtcctaca ctttttagga tgcttgggtga acataacacc acttataatg aacatccctg 180
gttcctatat tttgggctat gtgggtagga attgttactt gttactgcag cagcagccct 240
agaaagtaag cccagggtt cagatctaag ttagtcctaaa agctaaatga tttaaagtca 300
agttgtaatg ctaggcataa gcaactctata atacattaaa ttataggccg agcaattagg 360
gaatgtttct gaaacattaa acttgtattt atgtcactaa aattctaaca caaacttaaa 420
aaatgtgtct catacatatg ctgtactagg cttcatcatg catttctaaa tttgtgtatg 480
atttgaatat atgaaagaat ttatacaaga gtgttattta aaattattaa aaataaatgt 540
atataatttg tacctattgt aaaaa 565

<210> 198

<211> 484

<212> DNA

<213> Homo sapiens

<400> 198

tatgtaagta ttggtgtctg ctttaaaaaa ggagaccag acttcacctg tcctttttaa 60
acatttgaga acagtgttac tctgagcagt tgggccacct tcaccttata cgacagctga 120
ctgttgatg tgtccattgt cgccagtttg gctgttgccc ggacaggaca ggacctccat 180
tgggcgcagc agcaggtggc aggggtgtgg cttgaggtgg gtggcagcgt ctggtcctcc 240
tctctgtgtc tttctgagag ggtctctaaa gcagagtgtg gttggcctgg gggaaggcag 300
agcacgtatt tctccctctc agtacctctg catttgtgag tgttccctct ggctttctga 360
agggcagcag actcttgagt atactgcaga ggacatgctt tatcagtagg tcctgagggc 420
tccaggggct caactgacca agtaacacag aagttggggg atgtggccta tttgggtcgg 480
aaac 484

<210> 199

<211> 429

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 77, 88, 134, 151, 189, 227, 274, 319

<223> n = A,T,C or G

<400> 199

gcttatgttt tttgttttaa cttttgtttt ttaacattta gaatattaca ttttgtatta 60
tacagtacct ttctcanaca ttttgtanaa ttcatttcgg cagctcacta ggattttgct 120
gaacattaaa aagngtgata gcgatattag ngccaatcaa atggaaaaaa ggtagtctta 180

ataaacaana cacaacgttt ttatacaaca tacttttaaaa tattaanaaa actccttaat 240
attgttttctt attaagtatt attcttttggg caanattttc tgatgtttt gatttttctt 300
caatttagca tttgtcttng gtttttttct ctatttagca ttctgttaag gcacaaaaac 360
tatgtactgt atgggaaatg ttgtaaatat taccttttcc acatttttaa cagacaactt 420
tgaatccaa 429

<210> 200

<211> 279

<212> DNA

<213> Homo sapiens

<400> 200

gcttttttga ggaattacag ggaagctcct ggaattgtac atggatatct ttatccctag 60
ggggaaatca aggagctggg cacccttaat tctttatgga agtgtttaaa actatttttaa 120
ttttattaca agtattacta gagtagtggt tctactctaa gatttcaaaa gtgcatttaa 180
aatcatatcat gttcccgctt gcaaatatat tgttattttg gtggagaaaa aaatagtata 240
ttctacataa aaaattaaag atattaacta agaaaaaaa 279

<210> 201

<211> 569

<212> DNA

<213> Homo sapiens

<400> 201

taggtcagta ttttttagaaa ctcttaatag ctcatactct tgataccaaa agcagccctg 60
attgttaaag cacacacctg cacaagaagc agtgatgggt gcattttacat ttcttgggtg 120
cacaaaaaaa aattctcaaa aagcaaggac ttacgttttt tgcaaagcct ttgagaagtt 180
actggatcat aggaagctta taacaagaat ggaagattct taaataactc actttctttg 240
gtatccagta acagtagatg ttcaaaatat gtagctgatt aataccagca ttgtgaacgc 300
tgtacaacct tgtggttatt actaagcaag ttactactag cttctgaaaa gtagcttcat 360
aattaatggt atttatacac tgccttccat gacttttact ttgccctaag ctaatctcca 420
aaatctgaaa tgctactcca atatcagaaa aaaaggggga ggtggaatta tatttcctgt 480
gatttttaaga gtacagagaa tcatgcacat ctctgattag ttcatatatg tctagtgtgt 540
aataaaagtc aaagatgaac tctcaaaaa 569

<210> 202

<211> 501

<212> DNA

<213> Homo sapiens

<400> 202

attaatagtc ttaataattg ttggcaagga tccttttgct ttctttggca tgcaagctcc 60
tagcatctgg cagtggggcc aagaaaataa ggtttatgca tgtatgatgg ttttcttctt 120
gagcaacatg attgagaacc agtgatgtc aacaggtgca tttgagataa ctttaaatga 180
tgtacctgtg tggcttaagc tggaaatctg tcaccttcca tccatgcaac aacttggtca 240
aattcttgac aatgaaatga agctcaatgt gcatatggat tcaatccac accatcgatc 300
atagcaccac ctatcagcac tgaaaactct tttgcattaa gggatcattg caagagcagc 360
gtgactgaca ttatgaaggc ctgtactgaa gacagcaagc tgttagtaca gaccagatgc 420
tttcttggca ggctcgttgt acctcttggg aaacctcaat gcaagatagt gtttcagtgc 480
tggcatattt tggaaattctg c 501

<210> 203

<211> 261

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 36, 96

<223> n = A,T,C or G

<400> 203

```
gacaagctcc tggctcttgag atgtcttctc gttaangaga tgggcctttt ggaggtaaag 60
gataaaatga atgagttctg tcatgattca ctattntata acttgcatga cctttactgt 120
gttagctctt tgaatgttct tgaaatttta gactttcttt gtaaacaaat gatatgtcct 180
tatcattgta taaaagctgt tatgtgcaac agtgtggaga ttccttgtct gatttaataa 240
aataacttaaa cactgaaaaa a 261
```

<210> 204

<211> 421

<212> DNA

<213> Homo sapiens

<400> 204

```
agcatctttt ctacaacggt aaaattgcag aagtagctta tcattaaaaa acaacaacaa 60
caacaataac aataaatcct aagtgtaaat cagttattct accccctacc aaggatatca 120
gcctgttttt tccctttttt ctctctggaa taattgtggg ctctctccca aatttctaca 180
gcctctttcc tcttctcatg cttgagcttc cctgtttgca cgcatgcgtg tgcaggactg 240
gcttgtgtgc ttggactcgg ctccaggtgg aagcatgctt tcccttggtt ctgttggaga 300
aactcaaacc ttcaagccct aggtgtagcc attttgtcaa gtcacaaact gtatttttgt 360
actggcatta acaaaaaaag aagataaaat attgtaccat taaactttaa taaaacttta 420
a 421
```

<210> 205

<211> 460

<212> DNA

<213> Homo sapiens

<400> 205

```
tactctcaca atgaaggacc tggaatgaaa aatctgtgtc taaacaagtc ctctttagat 60
tttagtgcaa atccagagcc agcgtcgggt gcctcgagta attctttcat gggtagcttt 120
ggaaaagctc tcaggagacc tcacctagat gcctattcaa gctttggaca gccatcagat 180
tgtcagccaa gagcctttta tttgaaagct cattcttccc cagacttgga ctctgggtca 240
gaggaagatg ggaaagaaag gacagathtt caggaagaaa atcacatttg tacctttaaa 300
cagactttag aaaactacag gactccaaat tttcagtcct atgacttgga cacatagact 360
gaatgagacc aaaggaaaag cttaacatac tacctcaagg tgaactttta tttaaaagag 420
agagaatctt atgtttttta aatggaggtta tgaattttta 460
```

<210> 206

<211> 481

<212> DNA

<213> Homo sapiens

<400> 206

```
tgtggtggaa ttcgggacgc cccagaccc tgacttttct ctgcgtgggc cgtctcctcc 60
tgcggaagca gtgacctctg acccttggtg accttcgctt tgagtgcctt ttgaacgctg 120
gtcccgcggg acttggtttt ctcaagctct gtctgtccaa agacgctccg gtcgaggtcc 180
cgccctgccct ggttggtatc ttgaacccca gacgccctc tgtgctgctg tgtccggagg 240
cgcccttccc atctgcctgc ccaccggag ctctttccgc cgccgcaggg tcccaagccc 300
acctcccgcc ctcagtcctg cgggtgtcgt ctgggcacgt cctgcacaca caatgcaagt 360
cctggcctcc gcgccgccc gccacgcga gcgtacccg ccgccaactc tgttatttat 420
ggtgtgaccc cctggaggtg cctcgcggcc accggggcta tttattgttt aatttatttg 480
t 481
```

<210> 207

<211> 605

<221> misc_feature
<222> 20, 21, 61
<223> n = A,T,C or G

<400> 210
cgcccttgggg agccggcggn ngagtccggg acgtggagac ccgggggtccc ggcagccggg 60
nggcccgcgg gccaggggtg gggatgcacc gccgcggggt gggagctggc gccatcgcca 120
agaagaaact tgcagaggcc aagtataagg agcgagggac ggtcttggct gaggaccagc 180
tagcccagat gtcaaagcag ttggacatgt tcaaagaccaa cctggaggaa ttgtccagca 240
aacacaagca ggagatccgg aagaatcctg agttccgtgt gcagttccag gacatgtgtg 300
caaccattgg cgtggatccg ctggcctctg gaaaaggatt ttggtctgag atgctgggcg 360
tgggggactt ctattacgaa ctagggtgtcc aaattatcga agtgtgcctg gcgctgaagc 420
atcggaatgg aggtctgata actttggagg aactacatca acaggtgttg aagggaaggg 480
gcaagttcgc ccaggatgtc agtcaagatg acctgatcag agccatcaag aaa 533

<210> 211
<211> 451
<212> DNA
<213> Homo sapiens

<400> 211
ttagcttgag ccgagaacga ggcgagaaag ctggagaccg aggagaccgc ctagagcgga 60
gtgaacgggg aggggaccgt ggggaccggc ttgatcgtgc gcggacacct gctaccaagc 120
ggagcttcag caagggaagt gagggagcga gtagagaacg gccctcccag cctgaggggc 180
tgcgcaaggc agctagcctc acggaggatc gggaccgtgg gcgggatgcc gtgaagcgag 240
aagctgccct acccccagtg agccccctga aggcggctct ctctgaggag gaggtagaga 300
agaaatccaa ggctatcatt gaggaatata tccatctcaa tgacatgaaa gaggcagtcc 360
agtgcgtgca ggagctggcc tcacctcctc tgctcttcat ctttgtacgg catggtgtcg 420
agtctacgct ggagcgcagt gccattgctc g 451

<210> 212
<211> 471
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 54
<223> n = A,T,C or G

<400> 212
gtgattattc ttgatcaggg agaagatcat ttagatttgt tttgcattcc ttanaatgga 60
gggcaacatt ccacagctgc cctggctgtg atgagtgtcc ttgcaggggc cggagtagga 120
gcaactgggt gggggcggaa ttggggttac tcgatgtaag ggattccttg ttgttgtgtt 180
gagatccagt gcagttgtga tttctgtgga tcccagcttg gttccaggaa ttttgtgtga 240
ttggcttaaa tcagtttttc aatcttcgac agctgggctg gaacgtgaac tcagtagctg 300
aacctgtctg acccggtcac gttcttgat cctcagaact ctttgcctt gtcgggggtg 360
gggtgggaac tcacgtggg agcgggtgct gagaaaatgt aaggattctg gaatacatat 420
tccatgggac tttccttccc tctcctgctt cctcttttcc tgctccctaa c 471

<210> 213
<211> 511
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 27, 63, 337, 442

<212> DNA

<213> Homo sapiens

<400> 207

```
accctttttg gattcagggc tctcacaat taaaatgagt gtaatgaaac aagggtgaaa 60
tatagaagca tcccttttga tactgttttg ctacttacag tgtacttggc attgctttat 120
ctcactggat tctcacggta ggatttctga gatcttaatc taagctccaa agttgtctac 180
ttttttgata ctagggtgct ccttttggtt tacagagcag ggtcacttga tttgctagct 240
ggtggcagaa ttggcaccat taccaggtc tgactgacca ccagtcagag gcactttatt 300
tgtatcatga aatgatttga aatcatgtga aagcagcgaa gtctgataat gaatgccagc 360
tttccttgtg ctttgataac aaagactcca aatattctgg agaacctgga taaaagtgtg 420
aagggtctaga ttgggatttg aagacaaaat tgtaggaaat cttacatttt tgcaataaca 480
aacattaatg aaagcaaac attataaaag taattttaat tcaccacata cttatcaatt 540
tcttgatgct tccaaatgac atctaccaga tatggttttg tggacatctt tttctgttta 600
cataa 605
```

<210> 208

<211> 655

<212> DNA

<213> Homo sapiens

<400> 208

```
ggcgttgttc tggattcccg tcgtaactta aagggaact ttcacaatgt ccggagocct 60
tgatgtctcg caaatgaagg aggaggatgt ccttaagtgc cttgcagcag gaaccactt 120
agggtggcacc aatcttgact tccagatgga acagtacatc tataaaagga aaagtgtatg 180
catctatatc ataaatctca agaggacctg ggagaagctt ctgctggcag ctcgtgcaat 240
tgttgccatt gaaaaccctg ctgatgtcag tgttatatcc tccaggaata ctggccagag 300
ggctgtgctg aagtttgctg ctgccactgg agccactcca attgctggcc gcttcaactc 360
tggaaccttc actaaccaga tccaggcagc cttccgggag ccacggcttc ttgtggttac 420
tgaccccgag gctgaccacc agcctctcac ggaggcatct tatgttaacc tacctacct 480
tgcgctgtgt aacacagatt ctctctgcg ctatgtggac attgccatcc catgcaacaa 540
caagggagct cactcagtg gtttgatgtg gtggatgctg gctcgggaag ttctgcgcac 600
gcgtggcacc atttcccgct aacacccatg ggaggatcat cctgatctgt acttc 655
```

<210> 209

<211> 621

<212> DNA

<213> Homo sapiens

<400> 209

```
catttagaac atggttatca tccaagacta ctctaccctg caacattgaa ctccaagag 60
caaatccaca ttcctcttga gttctgcagc ttctgtgtaa atagggcagc tgcgtctat 120
gccgtagaat cacatgatct gaggaccatt catggaagct gctaaatagc ctagtctggg 180
gagtcctcca taaagttttg catggagcaa acaaacagga ttaaaactagg tttggttcct 240
tcagccctct aaaaagcatag ggcttagcct gcaggcttcc ttgggcttcc tctgtgtgtg 300
tagttttgta aacactatag catctgttaa gatccagtgt ccatggaaac cttcccat 360
gccgtgactc tggactatat cagtttttgg aaagcagggt tcctctgcct gctaacaagc 420
ccacgtggac cagtctgaat gtctttcctt tacacctatg tttttaataa gtcaaacctc 480
aagaaacaat ctaaacaagt ttctgttgca tatgtgtttg tgaacttgta tttgtattta 540
gtaggcttct atattgcatt taacttggtt ttgtaactcc tgattcttcc ttttcggata 600
ctattgatga ataaagaaat t 621
```

<210> 210

<211> 533

<212> DNA

<213> Homo sapiens

<220>

<223> n = A,T,C or G

<400> 213

```
ctaattagaa acttgctgta ctttttnttt tcttttaggg gtcaaggacc ctctttatag 60
ctnccatttg cctacaataa attattgcag cagtttgcaa tactaaaata ttttttatag 120
acttttatatt ttctcttttg ataaagggat gctgcatagt agagttgggt taattaaact 180
atctcagccg ttccctgctt ttcccttctg ctccatatgc ctcatgtgcc ttccaggag 240
ctcttttaat cttaaagttc tacatttcat gctcttagtc aaattctgtt acctttttaa 300
taactcttcc cactgcataat ttccatcttg aattgngngt tctaaattct gaaactgtag 360
ttgagataca gctattttaat atttctggga gatgtgcac cctcttcttt gtggttgccc 420
aagggttgtt tgcgtaactg anactccttg atatgcttca gagaatttag gcaaactg 480
gccatggccg tgggagtact gggagtaaaa t 511
```

<210> 214

<211> 521

<212> DNA

<213> Homo sapiens

<400> 214

```
agcattgcc aataatccct aattttccac taaaaatata atgaaatgat gttaagcttt 60
ttgaaaagtt taggttaaac ctactgttgt tagattaatg tatttggtgc ttccctttat 120
ctggaatgtg gcattagctt ttttatttta accctcttta attcttattc aattccatga 180
cttaagggtg gagagctaaa cactgggatt ttgggataac agactgacag ttttgcataa 240
ttataatcgg cattgtacat agaaaggata tggctacctt ttgttaaatc tgcactttct 300
aaatatcaaa aaagggaaat gaagtataaa tcaatttttg tataatctgt ttgaaacatg 360
agtttttatt gcttaatat agggctttgc cctttttctg taagtctctt gggatctgt 420
gtagaagctg ttctcattaa acaccaaaca gttaagtcca ttctctggta ctagctacaa 480
attcggtttc atattctact taacaattta aataaactga a 521
```

<210> 215

<211> 381

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> 17, 20, 60, 61, 365

<223> n = A,T,C or G

<400> 215

```
gagcggagag cggaccngtn agagccctga gcagccccac cgccgcccgc ggcctagttn 60
ncatcacacc ccgggaggag ccgcagctgc cgcagccggc cccagtcacc atcacgcaa 120
ccatgagcag cgaggccgag acccagcagc cgcccgcgc ccccccgcc gccccgcgc 180
tcagcgccgc cgacaccaag cccggcacta cgggcagcgg cgcagggagc ggtggcccg 240
gcggcctcac atcggcggcg cctgccggcg gggacaagaa ggtcatcgca acgaagggtt 300
tgggaaacagt aaaatgggtc aatgtaagga acggatatgg ttcatcaac aggaatgaca 360
ccaangaaga tgtatttgta c 381
```

<210> 216

<211> 425

<212> DNA

<213> Homo sapiens

<400> 216

```
ttactaacta ggtcattcaa ggaagtcaag ttaacttaaa catgtcacct aaatgcactt 60
gatggtgttg aaatgtccac cttcttaaat ttttaagatg aacttagttc taaagaagat 120
aacaggccaa tctgaagggt actccctgtt tgctgcagaa tgctagatat tttggatgtt 180
gcataagagt cctatttgcc ccagttaatt caacttttgt ctgcctgttt tgtggactgg 240
```

```
ctggctctgt tagaactctg tccaaaaagt gcatggaata taacttgtaa agcttccac 300
aattgacaat atatatgcat gtgtttaaac caaatccaga aagcttaaac aatagagctg 360
cataatagta tttattaaag aatcacaaact gtaaacaatga gaataactta aggattctag 420
ttag 425
```

<210> 217
<211> 181
<212> DNA
<213> Homo sapiens

```
<400> 217
gagaaaccaa atgataggtt gtagagcctg atgactccaa acaaagccat caccgcatt 60
cttctcctt cttctgggtg tacagctcca agggcccttc accttcatgt ctgaaatgga 120
actttggctt tttcagtga agaatatgt gaaggtttca tttgttcta gaaaaaaaaa 180
a 181
```

<210> 218
<211> 405
<212> DNA
<213> Homo sapiens

```
<400> 218
caggccttcc agttcactga caaacatggg gaagtgtgcc cagctggctg gaaacctggc 60
agtataacca tcaagcctga tgtccaaaag agcaaagaat atttctccaa gcagaagtga 120
gcgctgggct gtttttagtg caggctgcgg tgggcagcca tgagaacaaa acctcttctg 180
tatttttttt ttccattagt aaaacacaag acttcagatt cagccgaatt gtggtgtctt 240
acaaggcagg cctttcctac aggggtgtga gagaccagcc tttcttctt tggtaggaat 300
ggcctgagtt ggcgttgttg gcaggctact gttttgtatg atgtattagt agagcaaccc 360
attaatcttt tgtagtttgt attaaacttg aactgagaaa aaaaa 405
```

<210> 219
<211> 216
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 207, 210
<223> n = A,T,C or G

```
<400> 219
actccaagag ttagggcagc agagtggagc gatttagaaa gaacatttta aaacaatcag 60
ttaatttacc atgtaaaatt gctgtaaatg ataattgtga cagattttct gttcaaatat 120
tcaattgtaa acttcttggt aagactgtta cgtttctatt gcttttgtat gggatattgc 180
aaaaataaaa aggaaagaac cctcttnaan aaaaaa 216
```

<210> 220
<211> 380
<212> DNA
<213> Homo sapiens

```
<400> 220
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380

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<212> DNA

<213> Homo sapiens

<400> 221

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<211> 301

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 49, 64

<223> n = A,T,C or G

<400> 222

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<211> 200

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<213> Homo sapiens

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<211> 385

<212> DNA

<213> Homo sapiens

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<400> 225

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Ser Asp Glu Asn Asp Trp Asn Glu Lys Leu Tyr Pro Val Trp Lys Arg
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Gly Asp Met Arg Trp Lys Asn Ser Trp Lys Gly Gly Arg Val Gln Ala
65          70          75          80
Val Leu Thr Ser Asp Ser Pro Ala Leu Val Gly Ser Asn Ile Thr Phe
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Ala Val Asn Leu Ile Phe Pro Arg Cys Gln Lys Glu Asp Ala Asn Gly
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Asn Ile Val Tyr Glu Lys Asn Cys Arg Asn Glu Ala Gly Leu Ser Ala
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Asp Pro Tyr Val Tyr Asn Trp Thr Ala Trp Ser Glu Asp Ser Asp Gly
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Glu Asn Gly Thr Gly Gln Ser His His Asn Val Phe Pro Asp Gly Lys
145          150          155          160
Pro Phe Pro His His Pro Gly Trp Arg Arg Trp Asn Phe Ile Tyr Val
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Phe His Thr Leu Gly Gln Tyr Phe Gln Lys Leu Gly Arg Cys Ser Val
          180          185          190
Arg Val Ser Val Asn Thr Ala Asn Val Thr Leu Gly Pro Gln Leu Met
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Glu Val Thr Val Tyr Arg Arg His Gly Arg Ala Tyr Val Pro Ile Ala
210          215          220
Gln Val Lys Asp Val Tyr Val Val Thr Asp Gln Ile Pro Val Phe Val
225          230          235          240
Thr Met Phe Gln Lys Asn Asp Arg Asn Ser Ser Asp Glu Thr Phe Leu
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Lys Asp Leu Pro Ile Met Phe Asp Val Leu Ile His Asp Pro Ser His
          260          265          270
Phe Leu Asn Tyr Ser Thr Ile Asn Tyr Lys Trp Ser Phe Gly Asp Asn
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Thr Gly Leu Phe Val Ser Thr Asn His Thr Val Asn His Thr Tyr Val
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Leu Asn Gly Thr Phe Ser Leu Asn Leu Thr Val Lys Ala Ala Ala Pro
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Gly Pro Cys Pro Pro Pro Pro Pro Pro Arg Pro Ser Lys Pro Thr
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Pro Ser Leu Gly Pro Ala Gly Asp Asn Pro Leu Glu Leu Ser Arg Ile
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Pro Asp Glu Asn Cys Gln Ile Asn Arg Tyr Gly His Phe Gln Ala Thr
          355          360          365
Ile Thr Ile Val Glu Gly Ile Leu Glu Val Asn Ile Ile Gln Met Thr
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385          390          395          400
Val Val Thr Cys Gln Gly Ser Ile Pro Thr Glu Val Cys Thr Ile Ile

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1 5

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Gln Ile Ser Thr

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<400> 251

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<211> 153

<212> PRT

<213> Homo sapiens

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 35 40 45
 Ala Ala Val Ser Ser Ile Phe Asn Ser Pro Glu Glu Phe Leu Gly Lys
 50 55 60
 Ala Val Gly Leu Ser Ala Glu Ala Leu Thr Ile Gln Gln Tyr Ala Asp
 65 70 75 80
 Val Leu Ser Lys Ala Leu Gly Lys Glu Val Arg Asp Ala Lys Ile Thr
 85 90 95
 Pro Glu Ala Phe Glu Lys Leu Gly Phe Pro Ala Ala Lys Glu Ile Ala
 100 105 110
 Asn Met Cys Arg Phe Tyr Glu Met Lys Pro Asp Arg Asp Val Asn Leu
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<211> 462
<212> DNA
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gttcgatgag	tataacaatg	acaaaccttt	ctacataaat	gggcaaaatc	aaattaaagt	5580
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agaaaactgt attattagta agctttttaa agaaggatgc acctttatct acaatagcac 5700
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```

<210> 255

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> 9, 67, 247, 275, 277, 397

<223> n = A,T,C or G

<400> 255

```

gtggccagng actagaaggc gagggccgc gggaccatgg cggcgccggc ggacgagcgg 60
agtccanagg acggagaaga cgaggaagag gaggagcagt tggttctggt ggaattatca 120
ggaattattg attcagactt cctctcaaaa tgtgaaaata aatgcaaggt tttgggcatt 180
gacactgaga ggcccattct gcaagtggac agctgtgtct ttgctgggga gtatgaagac 240

```

actctangga cctgtgttat atttgaagaa aatgntnaac atgctgatac agaaggcaat 300
aataaaacag tgctaaaata taaatgccat acaatgaaga agctcagcat gacaagaact 360
ctcctgacag agaagaagga aggagaagaa aacatangtg g 401

<210> 256

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 7, 37, 51, 79, 96, 98, 103, 104, 107, 116, 167, 181, 183,
194, 206, 276, 303, 307, 308, 310, 323, 332, 341, 353, 374,
376

<223> n = A,T,C or G

<400> 256

tggtggnccct gggatgggga accgcggtgg ctcccgngga ggtttcggca ntggcatccg 60
gggccgggggt cgcggccgng gacggggcgg gggccnangc cgnnganctc gcggangcaa 120
ggccgaggat aaggagtggga tgcccgtcac caacttgggc cgcttgacca aggacatgaa 180
nancaagccc ctgnaggaga tctatntctt ctccctgcc ccattaagga atcaagagat 240
catttgattt ctccctgggg gcctctctca aggatnaggt ttttgaagat tatgccagt 300
canaaannan accccgttgc ccngtccatc tncacccaac ncttccaagg gcnatttttg 360
tttaggcctc attncngggg ggaaccttaa cccaatttgg g 401

<210> 257

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 382, 387

<223> n = A,T,C or G

<400> 257

atgtatgtaa aacacttcat aaaatgtaa gggctataac aaatatgtta taaagtgatt 60
ctctcagccc tgaggtatac agaatcattt gcctcagact gctgttgat tttaaaattt 120
ttaaaatatac tgctaagtaa tttgctatgt cttctccac actatcaata tgcctgcttc 180
taacaggctc ccactttct tttaatgtgc tgttatgagc tttggacatg agataaccgt 240
gcctgttcag agtgtctaca gtaagagctg gacaaaactct ggagggacac agtctttgag 300
acagctcttt tggttgcttt ccacttttct gaaaggttca cagtaacctt ctagataata 360
gaaactccca gttaaagcct angctancaa ttttttttag t 401

<210> 258

<211> 401

<212> DNA

<213> Homo sapiens

<400> 258

ggagcgctag gtcggtgtac gaccgagatt aggggtgcgtg ccagctccgg gagggccggg 60
tgagggggcgg ggcccaagct gccgaccga gccgatcgtc agggtcgcca gcgcctcagc 120
tctgtgagg agcagcagta gtcggaggggt gcaggatatt agaaatggct actccccagt 180
caattttcat ctttgcaatc tgcattttta tgataacaga attaatctg gcctcaaaaa 240
gctactatga tatcttaggt gtgccaaaat cgccatcaga gcgccaaatc aagaaggcct 300
ttcacaagtt ggccatgaag taccaccctg acaaaaaata gaccagatg ctgaagcaaa 360
attcagagag attgcagaag catatgaaac actctcagat g 401

<210> 259
<211> 401
<212> DNA
<213> Homo sapiens

<400> 259
attggggttg gaggaggat gatgacagag gaatgccctt tggccatcac ggttttgatt 60
ctccagaata ttgtgggttt gatcatcaat gcagtcagt taggctgcat tttcatgaaa 120
acagctcagg ctcacagaag ggcagaaact ttgattttca gccgccatgc tgtgattgcc 180
gtccgaaatg gcaagctgtg cttcatgttc cgagtgggtg acctgaggaa aagcatgac 240
attagtgcct ctgtgcgcat ccagggtggtc aagaaaacaa ctacacctga aggggaggtg 300
gttcctattc accaactgga cattcctgtt gataacccaa tcgagagcaa taacattttt 360
ctggtggccc ctttgatcat ctgccacgtg attgacaagc g 401

<210> 260
<211> 363
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 7, 9, 19, 41, 63, 73, 106, 111, 113, 116, 119, 156, 158,
162, 187, 247, 288, 289, 290, 292, 298, 299, 300, 340
<223> n = A,T,C or G

<400> 260
aggaganang gagggggana tgaataggga tggagagggga natagtggat gagcagggca 60
canggagagg aancagaaag gagaggcaag acaggggagac acacancaca nangangana 120
caggtggggg ctgggggtggg gcatggagag cctttnangt cncccaggcc accctgctct 180
cgctgggnctg ttgaaaccca ctccatggct tcctgccact gcagttgggc ccagggctgg 240
cttattnctg gaatgcaagt ggctgtggct tggagcctcc cctctggnnn anggaaannn 300
attgctccct tatctgcttg gaatatctga gtttttccan cccggaata aaacacacac 360
aca 363

<210> 261
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 114, 152
<223> n = A,T,C or G

<400> 261
cggctctccg ccgctctccc ggggtttcgg ggcacttggg tcccacagtc tggctctgct 60
tcaccttccc ctgacctgag tagtcgccat ggcacagggt ctcagaggca ctgngactga 120
cttccctgga tttgatgagc gggtgatgc anaaactctt cggaaggcta tgaaaggctt 180
gggcacagat gaggagagca tcctgactct gttgacatcc cgaagtaatg ctcagcgcca 240
ggaaatctct gcagctttta agactctgtt tggcagggat cttctggatg acctgaaatc 300
agaactaact ggaaaatttg aaaaattaat tgtggctctg atgaaaccct ctcggcttta 360
tgatgcttat gaactgaaac atgccttgaa gggagctgga a 401

<210> 262
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 7, 26, 258, 305, 358, 373, 374, 378
<223> n = A,T,C or G

<400> 262
agtctanaac atttctaata ttttngnctt tcatatatca aaggagatta tgtgaaacta 60
tttttaaata ctgtaaagtg acatatagtt ataagatata tttctgtaca gtagagaaag 120
agtttataac atgaagaata ttgtaccatt atacattttc attctcgatc tcataagaaa 180
ttcaaaagaa taatgataga ggtgaaaata tgtttacttt ctctaaatca agcctagtgt 240
tcaactcaaa aattatgntg catagtttta ttttgaattt aggttttggg actacttttt 300
tccancttca atgagaaaat aaaatctaca actcaggagt tactacagaa gttctaanta 360
tttttttgct aannagcnaa aaatataaac atatgaaaat g 401

<210> 263
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 232, 290, 304, 326, 383
<223> n = A,T,C or G

<400> 263
ctgtccgacc aagagaggcc ggccgagccc gaggtttggg cttttgcttt ctggcggagg 60
gatctgcggc ggtttaggag gcggcgctga tcctgggagg aagaggcagc tacggcggcg 120
gcggcggttg cggctagggc ggccgcgaat aaagggggcg ccgccgggtg atgcggtgac 180
cactgcgcca ggcccaggag ctgagtgggc cccggccctc agcccgtccc gncggacccg 240
ctttcctcaa ctctccatct tctcctgccg accgagatcg ccgaggcggn ctcaggctcc 300
ctanccctt ccccgctcct tccccncccc cgtccccgcc ccggggggcg ccgccaccgg 360
cctccacca tggctctgaa ganaatccac aaggaattga a 401

<210> 264
<211> 401
<212> DNA
<213> Homo sapiens

<400> 264
aacaccagcc actccaggac ccctgaaggc ctctaccagg tcaccagtgt tctgcgccta 60
aagccacccc ctggcagaaa cttcagctgt gtgttctgga atactcacgt gagggaaactt 120
actttggcca gcattgacct tcaaagtcag atggaaccca ggacccatcc aacttggtg 180
cttcacattt tcatcccctc ctgcacattt gctttcattt tcatagccac agtgatagcc 240
ctaagaaaac aactctgtca aaagctgtat tcttcaaaag acacaacaaa aagacctgtc 300
accacaacaa agaggggaagt gaacagtgtc gtgaatctga acctgtggtc ttgggagcca 360
gggtgacctg atatgacatc taaagaagct tctggactct g 401

<210> 265
<211> 271
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 59
<223> n = A,T,C or G

<400> 265

```
gccacttcct gtggacatgg gcagagcgct gctgccagtt cctggtagcc ttgaccacna 60
cgctgggggg tctttgtgat ggtoatgggt ctcatttgca cttgggggtg tgggattcaa 120
gttagaagtt tctagatctg gccgggcgca gtggctcaca cctgtaatcc cagcacttta 180
ggaggctgag gcaggcggat catgaggtca ggagatcgag accgtcctgg ctaacacagt 240
gaaaccccgct ctctactaaa aatacaaaaa a 271
```

<210> 266

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 45

<223> n = A,T,C or G

<400> 266

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attcataaat ttagctgaaa gatactgatt caatttgtat acagngaata taaatgagac 60
gacagcaaaa ttttcatgaa atgtaaaata tttttatagt ttgttcatac tatatgaggt 120
tctatttttaa atgactttct ggatttttaa aaatttcttt aaatacaatc atttttgtaa 180
tattttatttt atgcttatga tctagataat tgcagaatat cattttatct gactctgtct 240
tcataagaga gctgtggccg aattttgaac atctgttata gggagtgatc aaattagaag 300
gcaatgtgga aaaacaattc tgggaaagat ttctttatat gaagtcctcg ccactagcca 360
gccatcctaa ttgatgaaag ttatctgttc acaggcctgc a 401
```

<210> 267

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 116, 247, 277, 296, 307, 313, 322, 323, 336, 342, 355, 365, 377, 378, 397

<223> n = A,T,C or G

<400> 267

```
gaagaggcat cacctgatcc cggagacctt tggagttaag aggcggcgga agcgagggcc 60
tgtggagtcg gacctctctc ggggtgagcc agggtcggcg cgcgcggctg tctcanaact 120
catgcagctg ttcccgcgag gcctgtttga ggacgcgctg ccgcccatcg tgctgaggag 180
ccagggtgtac agccttgtgc ctgacaggac cgtggccgac cggcagctga aggagcttca 240
agagcanggg gagacaaaat cgtccagctg ggcttcnact tggatgccca tggaanttat 300
tctttcnctt ganggactta cnngggaccc aagaanccct tncaaggggc ccttngtgga 360
tgggncccg aaccccnnta tttgcccttg ggggggncca a 401
```

<210> 268

<211> 223

<212> DNA

<213> Homo sapiens

<400> 268

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tcgccatggt ggccaggctg gtottgaact cctgacttta agtgatccac ccgcctcaac 60
ctcccaaagt gctgggatta cagggtgtgag ccaccgcgcc tggcctgata catactttta 120
gaatcaagta gtcacgcact ttttctgttc atttttctaa aaagtaaata tacaatggtt 180
ttgttttttg ttttttttgt ttgtttgttt ctgttttttt ttt 223
```

<210> 269

<211> 401

<212> DNA

<213> Homo sapiens

<400> 269

```
actatgtaaa ccacattgta ctttttttta ctttggaac aaatatttat acatacaaga 60
tgctagttca tttgaatatt tctcccaact tatccaagga tctccagctc taacaaaatg 120
gtttattttt atttaaatgt caatagttgt tttttaaaat ccaaatacaga ggtgcaggcc 180
accagttaaa tgccgtctat caggttttgt gccttaagag actacagagt caaagctcat 240
ttttaaaagga gtaggacaaa gttgtcacag gtttttgttg ttgtttttat tgcccccata 300
attacatggt aatttcatt tatatcaggg attctattta cttgaagact gtgaagttgc 360
cattttgtct cattgttttc tttgacataa ctaggatcca t 401
```

<210> 270

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 240, 382

<223> n = A,T,C or G

<400> 270

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tggtgttga ttcacctcag cactgcttgg tatctgcacc ctacctctct ttagaggctg 60
ccttgtcaac tgaaaaatgc acctgacttc gagcaagact ctttccttag gttctggatc 120
tgtttgagcc ccatggcact gagctggaat ctgagggtct tgttccaagg atgtgatgat 180
gtgggagaat gttctttgaa agagcagaaa tccagtctgc atggaaacag cctgtagagn 240
agaagtttcc agtgataagt gttcactgtt ctaaggaggt acaccacagc tacctgaatt 300
ttcccaaaat gagtgttctc gtgcgttaca actggccttt gtacttgact gtgatgactt 360
tgttttttct tttcaattct anatgaacat gggaaaaaat g 401
```

<210> 271

<211> 329

<212> DNA

<213> Homo sapiens

<400> 271

```
ccacagcctc caagtcaggt ggggtggagt cccagagctg cacagggttt ggcccaagtt 60
tctaaggag gcacttctc ccctcgccca tcagtgccag cccctgctgg ctggtgcctg 120
agccctcag acagccccct gccccgagg cctgccttct cagggacttc tgcggggcct 180
gaggcaagcc atggagttag acccaggagc cggacacttc tcaggaaatg gcttttccca 240
acccccagcc cccaccgggt gggtcttctc gttctgtgac tgtgtatagt gccaccacag 300
cttatggcat ctcatggag acaaaaaaa 329
```

<210> 272

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 1, 7, 12, 21, 61, 62, 66, 72, 78, 88, 90, 92, 98, 117, 119,
128, 130, 134, 142, 144, 151, 159, 162, 164, 168, 169, 177,
184, 185, 188, 194, 202, 204, 209, 213, 218, 223, 231, 260,
272, 299, 300, 306, 321, 322, 323, 331, 335, 336, 338

<223> n = A,T,C or G

<221> misc_feature

<222> 341, 342, 343, 345, 346, 351, 358, 360, 362, 363, 387, 390,
392

<223> n = A,T,C or G

<400> 272

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nggctgntaa cntcgagagt nacttcctgg actatcctgg agacccccctc cgcttcacag 60
nncatnatac cntcatngc tggggccntn angacacnat cccactccaa cacctgngng 120
atgctggncn cctnggaacc ancntcagaa ngaccctgnt cntntgtntt ccgcaanctg 180
aagannaangc gggntacacc tncntgcant ggnccacnct gcnggggaact ntacacacct 240
acgggatgtg gctgcgccan gagccaagag cntttctgga tgattcccca gcctcttggn 300
agggantcta caacattgct nnntacctt ntcnncngc nnntnntgga ntacaggngn 360
tnntaacact acatcttttt tactgcncn tncctgggtg g 401

```

<210> 273

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 399

<223> n = A,T,C or G

<400> 273

```

cagcaccatg aagatcaaga tcatcgcacc cccagagcgc aagtactcgg tgtggatcgg 60
tggtccatc ctggcctcac tgtccacctt ccagcagatg tggattagca agcaggagta 120
cgacgagtcg ggcccctcca tctgccaccg caaatgcttc taaacggact cagcagatgc 180
gtagcatttg ctgcatgggt taattgagaa tagaaatttg cccctggcaa atgcacacac 240
ctcatgctag cctcacgaaa ctggaataag ccttcgaaaa gaaattgtcc ttgaagcttg 300
tatctgatat cagcactgga ttgtagaact tgttgctgat tttagccttg tattgaagtt 360
aactgttccc cttgttatta acgtgtcagg gctgagtgnt c 401

```

<210> 274

<211> 401

<212> DNA

<213> Homo sapiens

<400> 274

```

ccaccacac ccaccgcgc ctcgttcgcc tcttctccgg gagccagtc gcgccaccgc 60
cgccgcccag gccatcgcca cctccgcag ccatgtccac caggtccgtg tcctcgtcct 120
cctaccgcag gatgttcggc ggcccgggca ccgcgagccg gccgagctcc agccggagct 180
acgtgactac gtccaccgc acctacagcc tgggcagcgc gctgcgcccc agcaccagcc 240
gcagcctcta cgctcgtcc ccgggcggcg tgtatgccac gcgtcctct gccgtgcgcc 300
tgccgagcag cgtgcccggg gtgcggctcc tgcaggactc ggtggacttc tcgctggccg 360
acgccatcaa caccgagttc aagaacaccc gcaccaacga g 401

```

<210> 275

<211> 401

<212> DNA

<213> Homo sapiens

<400> 275

```

ccacttccac cactttgtgg agcagtgcct tcagcgcaac ccggatgcc ggtatccctg 60
ctggcctggg cctgggcttc gggagagcag aggggtgctca ggagggtgta gccagggtgt 120
gaagggaactt acctcccaaa ggttctgcag ggggaatctgg agctacacac aggagggatc 180
agtcctggg tgtgtcagag gccagcctgg ggagctctgg cactgcttc ccatgagctg 240
agggagaggg agaggggacc cgaggctgag gcataagtgg caggatttcg ggaagctggg 300
gacacggcag tgatgctgcg gtctctctc cctttccct ccaggcccag tgccagcacc 360

```

ctcctgaacc actcttttctt caagcagatc aagcgacgtg c 401

<210> 276

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 11

<223> n = A,T,C or G

<400> 276

tctgatattg ntacccttga gccacctaag ttagaagaaa ttggaaatca agaagttgtc 60
attggtgaag aagcacagag ttcagaagac ttaacatgg gctcttctc tagcagccag 120
tatactttct gtcagccaga aactgtatct tcatctcagc ctagtgtatga tgaatcaagt 180
agtgtatgaaa ccagtaatca gccagtcct gccttttagac gacgccgtgc taggaagaag 240
accgttttctg cttcagaatc tgaagaccgg ctagtgtgtg aacaagaaac tgaaccttct 300
aaggagttga gtaaacgtca gttagtagt ggtctcaata agtgtgttat acttgctttg 360
gtgatgtcaa tcagcatggg atttgcccat ttctatggca c 401

<210> 277

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 227, 333

<223> n = A,T,C or G

<400> 277

aactttggca acatatctca gcaaaaacta cagctatggt attcatgcc aataaaaagc 60
tgtgcagagg agtggctgca atgaggtcac aacgggtgtg gatgtaaaag agatcttcaa 120
gtcctcatca cccatccctc gaactcaagt cccgctcatt acaaattctt cttgccagtg 180
tccacacatc ctgcccacac aagatgttct catcatgtgt tacgagnggc gctcaaggat 240
gatgcttctt gaaaattgct tagttgaaaa atggagagat cagcttagta aaagatccat 300
acagtgggaa gagaggctgc aggaacagcg ganaacagtt caggacaaga agaaaacagc 360
cgggcgcacc agtcgtagta atcccccaa accaaaggga a 401

<210> 278

<211> 401

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 322, 354

<223> n = A,T,C or G

<400> 278

aatgagtgtg agaccacaaa tgaatgccgg gaggatgaaa tgtgttgga ttatcatggc 60
ggcttccgtt gttatccacg aaatccttgt caagatccct acattctaac accagagaac 120
cgatgtgttt gccagtcctc aaatgccatg tgccgagaa tgccccagtc aatagtctac 180
aaatacatga gcatccgcatc tgataggtct gtgccatcag acatcttcca gatacaggcc 240
acaactatct atgccaacac catcaatact ttctggatta aatctggaaa tgaaaatgga 300
gagttctacct acgacaacaa anccctgtaa gtgcaatgct tgtgtctgtg aagncattat 360
caggaccaag agaacatatc gtggacctgg agatgctgac a 401

<210> 279
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 30, 35, 81, 88, 180, 212, 378, 384, 391
<223> n = A,T,C or G

<400> 279
aaattattgc ctctgatata tacctaagtn aacanaacat taatacctaa gtaaacataa 60
cattacttgg agggttgcag nttctaantg aaactgtatt tgaaactttt aagtatactt 120
taggaaacaa gcatgaacgg cagtctagaa taccagaaac atctacttgg gtagcttggn 180
gccattatcc tgtggaatct gatagtctg gnagcatgtc attgatggga catgaagaca 240
tcttttgaaa tgatgagatt atttcctgtg ttaaaaaaaa aaaaaatctt aaattcctac 300
aatgtgaaac tgaaactaat aattttgatc ctgatgtatg ggacagcgta tctgtaccag 360
gctctaaata acaaaagnta gggngacaag nacatgttcc t 401

<210> 280
<211> 326
<212> DNA
<213> Homo sapiens

<400> 280
gaagtggaaat tgtataattc aattcgataa ttgatctcat gggctttccc tggaggaaag 60
gttttttttt ttgttttttt tttaagaact tgaaacttgt aaactgagat gtctgtagct 120
tttttgccca tctgtagtgt atgtgaagat ttcaaaacct gagagcactt tttctttgtt 180
tagaattatg agaaaggcac tagatgactt taggatttgc atttttccct ttattgcctc 240
atttcttgtg acgccttggt ggggaggga atctgtttat ttttcctac aaataaaaag 300
ctaagattct atatcgcaaa aaaaaa 326

<210> 281
<211> 374
<212> DNA
<213> Homo sapiens

<400> 281
caacgcgttt gcaaatattc ccctggtagc ctacttcctt acccccgaat attggttaaga 60
tcgagcaatg gcttcaggac atgggttctc ttctcctgtg atcattcaag tgctcactgc 120
atgaagactg gcttgtctca gtgtttcaac ctcaccaggg ctgtctcttg gtccacacct 180
cgctccctgt tagtgccgta tgacagcccc catcaaatga ccttgcccaa gtcacgggtt 240
ctctgtggtc aaggtttggt ggctgattgg tggaaagtag ggtggaccaa aggaggccac 300
gtgagcagtc agcaccagtt ctgcaccagc agcgctccg tcctagtggg tgttcctgtt 360
tctcctggcc ctgg 374

<210> 282
<211> 404
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 26, 27, 51, 137, 180, 222
<223> n = A,T,C or G

<400> 282

```

agtgtggtgg aattcccgca tcctanncgc cgactcacac aaggcagagt ngccatggag 60
aaaattccag tgtcagcatt cttgtccctt gtggccctct cctacactct ggccagagat 120
accacagtca aacctgnagc caaaaaggac acaaaggact ctgcacccaa actgccccan 180
accctctcca gaggttgggg tgaccaactc atctggactc anacatatga agaagctcta 240
tataaatcca agacaagcaa caaaccttg atgattattc atcacttggg tgagtgccca 300
cacagtcaag ctttaaagaa agtgtttgct gaaaataaag aaatccagaa attggcagag 360
cagtttgtcc tcctcaatct ggtttatgaa acaactgaca aaca 404

```

```

<210> 283
<211> 184
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 26
<223> n = A,T,C or G

```

```

<400> 283
agtgtggtgg aattcacttg cttaanttgt gggcaaaaga gaaaaagaag gattgatcag 60
agcatttgtc aatacagttt cattaactoc ttccctcgct ccccäaaaa tttgaatttt 120
tttttcaaca ctcttacacc tgttatggaa aatgtcaacc tttgtaagaa aaccaaata 180
aaaa 184

```

```

<210> 284
<211> 421
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 147, 149
<223> n = A,T,C or G

```

```

<400> 284
ctattaatcc tgccacaata tttttaatta cgtacaaaga tctgacatgt caccagggg 60
cccatttcac ccactgctct gtttggccgc cagtcttttg tctctctctt cagcaatgg 120
gaggcggata ccctttcctc ggggaanana aatccatggg ttgttgcct tgccaataac 180
aaaaatgttg gaaagtcgag tggcaaagct gttgccattg gcatctttca cgtgaaccac 240
gtcaaaagat ccagggtgcc tctctctggt ggtgatcaca ccaattcttc ctagggttagc 300
acctccagtc accatacaca ggttaccagt gtcgaacttg atgaaatcag taatcttgcc 360
agtctctaaa tcaatctgaa tggatatcatt caccttgatg aggggatcgg ggtagcggat 420
g 421

```

```

<210> 285
<211> 361
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 34, 188
<223> n = A,T,C or G

```

```

<400> 285
ctgggtggta actctttatt tcattgtccg gaanaaagat gggagtggga acagggtgga 60
cactgtgcag gcttcagctt ccactccggg caggattcag gctatctggg accgcaggga 120
ctgccaggtg cacagccctg gctcccaggg caggcaggca aggtgacggg actggaagcc 180

```

```

cttttcanag ccttgaggga gctgggtccgt ccacaagcaa tgagtgccac tctgcagttt 240
gcaggggatg gataaacagg gaaacactgt gcattcctca cagccaacag tgtaggtctt 300
ggtgaagccc cggcgctgag ctaagctcag gctgttccag ggagccacga aactgcaggt 360
a 361

```

```

<210> 286
<211> 336
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 40, 68, 75, 127, 262
<223> n = A,T,C or G

```

```

<400> 286
tttgagtggc agcgcccttta tttgtggggg ccttcaaggn agggtcgtgg ggggcagcgg 60
ggaggaanag ccganaaaact gtgtgaccgg ggccctcaggt ggtgggcatt gggggctcct 120
cttgcanaatg cccattggca tcaccggtgc agccattggt ggcagcgggt accggtcctt 180
tcttgttcaa catagggtag gtggcagcca cgggtccaac tcgcttgagg ctgggccctg 240
ggcgctccat tttgtgttcc angagcatgt ggttctgtgg cgggagcccc acgcaggccc 300
tgaggatggt ctcgatgcag ctgcgtggc ggaaaa 336

```

```

<210> 287
<211> 301
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 15, 33, 44, 53, 76, 83, 107, 117, 154, 166, 192, 194, 207,
215, 241, 246
<223> n = A,T,C or G

```

```

<400> 287
tgggtaccaa atttntttat ttgaaggaat ggnacaaatc aaanaactta agnggatggt 60
ttgttacaac ttatanaaaa gnaaaaggaa accccaacat gcatgcnctg ccttggngac 120
caggggaagtc accccacggc tatggggaaa ttancccgag gcttancttt cattatcact 180
gtctcccagg gngngcttgt caaaaanata ttccnccaag ccaaattcgg gcgctcccat 240
nttgcncaag ttggtcacgt ggtcacccaa ttctttgatg gctttcacct gctcattcag 300
g 301

```

```

<210> 288
<211> 358
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 39, 143, 226
<223> n = A,T,C or G

```

```

<400> 288
aagtttttaa actttttatt tgcatattaa aaaaattgng cattccaata attaaaatca 60
tttgaacaaa aaaaaaaatg gcactctgat taaactgcat tacagcctgc aggacacctt 120
gggccagctt ggttttactc tanatttcac tgctgtccca cccacttct tccacccac 180
ttcttccttc accaacatgc aagttctttc ctccctgcc agccanatag atagacagat 240
gggaaaggca ggcgggcct tcgttgtcag tagttctttg atgtgaaagg ggcagcacag 300

```


tcattttaaac ttgatccaac ctctttgcat cttacaaagt taaacagcta aaagaagt 358

<210> 289

<211> 462

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 87, 141, 182, 220, 269, 327

<223> n = A,T,C or G

<400> 289

ggcatcagaa atgctgttta tttctctgct gctccaagc tggctggcct ttgcagagga 60
gcagacaaca gatgcatagt tgggganaaa gggaggacag gttccaggat agagggtgca 120
ggctgaggga ggaagggtaa naggaaggaa ggccatcctg gatccccaca tttcagtctc 180
anatgaggac aaagggactc ccaagccccc aaatcatcan aaaacaccaa ggagcaggag 240
gagcttgagc agggcccagg gagcctcana gccataccag ccaactgtcta cttcccatcc 300
tcctctccca ttccctgtct gtttcanacc acctcccagc taagccccag ctccattccc 360
ccaatcctgg cccttgccag cttgacagtc acagtgcctg gaattccacc actgaggctt 420
ctcccagttg gattaggacg tcgccctgtt agcatgctgc cc 462

<210> 290

<211> 481

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 44, 57, 122, 158, 304, 325, 352, 405

<223> n = A,T,C or G

<400> 290

tactttccta aactttatta aagaaaaaag caataagcaa tggnggtaaa tctctanaac 60
atacccaatt ttctgggctt cctccccga gaatgtgaca ttttgatttc caaacatgcc 120
anaagtgtat ggttccaac tgtactaaag taggtganaa gctgaagtcc tcaagtgttc 180
atcttccaac ttttccagct ctgtgtctg tctttggatc agcaataatt gcctgaacag 240
ctactatggc ttctgtgatt tttgtctgta gctctctgag ctctctatg tgcagcaatc 300
gcanaatttg agcagcttca ttaanaactg catctcctgt gtcaaaacca anaatatgtt 360
tgtctaaagc aacaggtaag ccctcttttg tttgatttgc cttancaact gcacacctgtg 420
tcaggcgctc ctgaaccaa atccgaattg ccttaagcat taccaggtaa tcatcatgac 480
g 481

<210> 291

<211> 381

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 79, 166, 187, 208, 219, 315

<223> n = A,T,C or G

<400> 291

tcatagtaat gtaaaacat ttgtttaatt ctaaatcaaa tcactttcac aacagtgaaa 60
attagtgact ggtaaggng tgccactgta catatcatca ttttctgact ggggtcagga 120
cctggctcta gtccacaagg gtggcaggag gaggggtggag gctaanaaca cagaaaacac 180
acaaaanaaa ggaaagctgc cttggcanaa ggatgaggng gtgagcttgc cgaaggatgg 240

```

tgggaagggg gctccctgtt ggggccgagc caggagtccc aagtcagctc tctgcctta 300
cttagctcct ggcanagggt gagtggggac ctacgaggtt caaaatcaaa tggcatttgg 360
ccagcctggc tttactaaca g                                     381

```

```

<210> 292
<211> 371
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 32, 55, 72, 151, 189, 292
<223> n = A,T,C or G

```

```

<400> 292
gaaaaaataa tccgtttaat tgaaaaacct gnaggatact attccactcc cccanattgag 60
gaggctgagg anaccaaacc cctacatcac ctctgtagcca cttctgatac tcttcacgag 120
gcagcaggca aagacaattc ccaaaacctc nacaaaagca attccaaggg ctgctgcagc 180
taccaccanc acatttttcc tcagccagcc cccaatcttc tccacacagc cctccttatg 240
gatcgccctc tcgttgaaat taatcccaca gccacagcta acattaatgc ancaggagtc 300
ggggactcgg ttcttcgaca tggaagggat tttctcccaa tctgtgtagt tagcagcccc 360
acagcactta a                                     371

```

```

<210> 293
<211> 361
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 75, 196, 222
<223> n = A,T,C or G

```

```

<400> 293
gattttaaag aaaacacttt attgttcagc aattaaaagt tagccaaata tgtatttttc 60
tccataattt attgngatgt tatcaacatc aagtaaaatg ctcatittca tcatttgctt 120
ctgttcattgt tttcttgaac acgtcttcaa ttttccttcc aaaatgctgc atgccacact 180
tgaggtaacg aagcanaagt atttttaaac atgacagcta anaacattca tctacagcaa 240
cctatatgct caatacatgc cgcgtgatcc tagtagtttt ttcacaacct tctacaagtt 300
tttggaaac atctgttatg atgactttca tacaccttca cctcaaaggc tttcttgcac 360
c

```

```

<210> 294
<211> 391
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> 26, 77, 96, 150, 203, 252, 254, 264, 276
<223> n = A,T,C or G

```

```

<400> 294
tatttttaaag ttttaattatg attcanaaaa aatcgagcga ataactttct ctgaaaaaat 60
atattgactc tgtatanacc acagttattg gggganaagg gctggtagg taaattatcc 120
tattttttat tctgaaaatg atattaatan aaagtcccg ttcagctctg attataaaga 180
tacaatgccc caaaatggct ganaataaat acaacaggaa atgcaaaagc tgtaaagcta 240
agggcatgca ananaaaatc tcanaatacc caaagnggca acaaggaacg tttggctgga 300

```

atttgaagtt atttcagtca tctttgtctt tggctccatg tttcaggatg cgtgtgaact 360
cgatgtaatt gaaattcccc tttttatcaa t 391

<210> 295
<211> 343
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 145, 174, 205, 232
<223> n = A,T,C or G

<400> 295
ttcttttgtt ttattgataa cagaaactgt gcataattac agatttgatg aggaatctgc 60
aaataataaa gaatgtgtct actgccagca aaatacaatt attccatgcc ctctcaacat 120
acaaatatag agttcttcac accanatggc tctgggtgtaa caaagccatt ttanatgttt 180
aattgtgctt ctacaaaacc ttcanagcat gaggtagttt cttttaccta cnatattttc 240
cacatttcca ttattacact tttagttagc taaaatcctt ttaacatagc ctgcggatga 300
tctttcacaa aagccaagcc tcatttataa aggggtttatt tct 343

<210> 296
<211> 241
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 96, 98, 106, 185
<223> n = A,T,C or G

<400> 296
ttcttggata ttggttggtt ttgtgaaaaa gtttttggtt ttcttctcag tcaactgaat 60
tatttctcta ctttgccctc ctgatgccca catgananaa cttaanataa tttctaacag 120
cttccacttt ggaaaaaaa aaaacctgtt ttccctcatgg aaccccagga gttgaaagt 180
gatanatgc tctcaaaatc taaggctctg ttcagcttta cattatgta cctgacgttt 240
t 241

<210> 297
<211> 391
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 12, 130
<223> n = A,T,C or G

<400> 297
gttgtggctg anaatgctgg agatgctcag ttctctccct cacaaggtag gccacaaatt 60
cttgggtggt ccctcacatc tggggtcttc aggcaccagc catgcctgcc gaggagtgt 120
gtcaggacan accatgtccg tgctaggccc aggcacagcc caaccactcc tcatccaagt 180
ctctcccagg tttctggtcc cgatgggcaa ggatgacccc tccagtggct ggtaccccac 240
catcccacta cccctcacat gctctcactc tccatcaggt ccccaatcct ggcttccctc 300
ttcacgaact ctcaagaaa aggaaggata aaacctaaat aaaccagaca gaagcagctc 360
tggaagagta caaaaagaca gccagaggtg t 391

<210> 298

<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 14, 30, 76, 116, 201, 288, 301
<223> n = A,T,C or G

<400> 298
caagccaaac tgtntccagc tttattaaan atactttcca taaacaatca tggatattca 60
ggcaggacat gggcanacaa tcgttaacag tatacaacaa ctttcaaact cccttnttca 120
atggactacc aaaaatcaaa aagccactat aaaacccaat gaagtcttca tctgatgctc 180
tgaacaggga aagtttaaag ngagggttga catttcacat ttagcatgtt gtttaacaac 240
ttttcacaaag ccgaccctga ctttcaggaa gtgaaatgaa aatggcanaa tttatctgaa 300
natccacaat ctaaaaatgg a 321

<210> 299
<211> 401
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 104, 268, 347
<223> n = A,T,C or G

<400> 299
tatcataaag agtgttgaag tttatttatt atagcaccat tgagacattt tgaaattgga 60
attggtaaaa aaataaaaaca aaaagcattt gaattgtatt tggnggaaca gcaaaaaaag 120
agaagtatca tttttctttg tcaaattata ctgtttccaa acattttgga aataaataac 180
tggaattttg tcggtcactt gcactgggtg acaagattag aacaagagga acacatatgg 240
agttaaattt tttttgttgg gatttcanat agagtgttgg ttataaaaag caaacagggc 300
caacgtccac accaaattct tgatcaggac caccaatgtc atagggngca atatctacaa 360
taggtagtct cacagccttg cgtgttcgat attcaaagac t 401

<210> 300
<211> 188
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 48
<223> n = A,T,C or G

<400> 300
tgaatgcttt gtcataattaa gaaagttaaa gtgcaataat gtttgaanac aataagtgg 60
ggtgtatctt gtttctaata agataaactt ttttgtcttt gctttatctt attagggagt 120
tgtatgtcag tgtataaaac atactgtgtg gtataacagg cttaataaat tctttaaaag 180
gaaaaaaa 188

<210> 301
<211> 291
<212> DNA
<213> Homo sapiens

<400> 301

```
aagatTTTgt tttatTTTat tatggctaga aagacactgt tatagccaaa atcggcaatg 60
acactaaaga aatcctctgt gctTTTcaat atgcaaatat atttcttcca agagttgccc 120
tggtgtgact tcaagagttc atgttaactt cttttctgga aacttccttt tcttagttgt 180
tgtattcttg aagagcctgg gccatgaaga gcttgccctaa gttttgggca gtgaactcct 240
tgatgttctg gcagtaagtg tttatctggc ctgcaatgag cagcgagtcc a 291
```

<210> 302

<211> 341

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 25

<223> n = A,T,C or G

<400> 302

```
tgatTTTtca taatTTTatt aaatnatcac tgggaaaact aatggttcgc gtatcacaca 60
attacactac aatctgatag gagtggtaaa accagccaat ggaatccagg taaagtacaa 120
aaacgccacc ttttattgtc ctgtcttatt tctcggaag gagggttcta ctttacacat 180
ttcatgagcc agcagtggac ttgagttaca atgtgtaggt tccttgtggg tatagctgca 240
gaagaagcca tcaaattctt gaggacttga catctctcgg aaagaagcaa actagtggat 300
ccccgggct gcaggaattc gatatcaagc ttatcgatac c 341
```

<210> 303

<211> 361

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 15, 27, 92, 124, 127, 183, 198, 244, 320

<223> n = A,T,C or G

<400> 303

```
tgcagacagt aaatnaattt tatttngtt cacagaacat actaggcgat ctcgacagtc 60
gtctccgtgac agccaccaa cccccaaccc tntacctcgc agccacccta aaggcgactt 120
caanaanatg gaaggatctc acggatctca ttcctaattg tccgcgaag tctcacacag 180
tanacagacg gatttganat gctggaggat gcagtcacct cctaaactta cgacccacca 240
ccanacttca tcccagccgg gacgtcctcc cccaccggag tcctcccat ttcttctcct 300
actttgccgc agttccaggn gtctgtcttc caccagtccc acaaagtca ataaatacca 360
a 361
```

<210> 304

<211> 301

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 23, 104, 192

<223> n = A,T,C or G

<400> 304

```
ctcttttcaa cagcctttat ttncggccct tgatcctgct cggatgctgg tggaggccct 60
tagctccgcc cgccaggctc tgtgccgcct ccccgaggc gcanattcat gaacacggtg 120
ctcaggggct tgaggcgta ctccccagc gggagctggg cctccagggg cttcccctcg 180
aaggtcagcc anaacaggtc gtcctgcaca ccctccagcc cgctcacttg ctgcttcagg 240
```

tggggccacgg tctgcgtcag ccgcacctcg taggtgctgc tgcggccctt gttattcttc 300
a 301

<210> 305
<211> 331
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 3, 36, 60, 193, 223
<223> n = A,T,C or G

<400> 305
ganaggctag taacatcagt tttattgggt tggggnggca accatagcct ggctgggggn 60
ggggctggcc ctcacaggtt gttgagttcc agcaggggtct ggtccaaggt ctggtgaatc 120
tcgacgttct cctccttggc actggccaag gtctcttcta ggtcatcgat ggttttctcc 180
aactttgcc aacacctctc ggcaactct gctcgggtct canctcctt cagcttctcc 240
tccaacaggt tgatctctc ttcataattt tcttcttgg gggaatactc ctcctctgag 300
gccatcaggg acttgagggc ctggtccatg g 331

<210> 306
<211> 457
<212> DNA
<213> Homo sapiens

<400> 306
aatatgtaaa ggtaataact tttattatat taaagacaat gcaaacgaaa aacagaattg 60
agcagtgcaa aattttaaagg actgttttgt totcaaagtt gcaagtttca aagccaaaag 120
aattatatgt atcaaatata taagtaaaaa aaagttagac ttccaagcct gtaatcccag 180
cactttggga ggctgaggca ggtggatcac taacattaaa aagacaacat tagattttgt 240
cgatttatag caattttata aatatataac tttgtcactt ggatcctgaa gcaaaataat 300
aaagtgaatt tgggattttt gtacttggtt aaaagttaa caccctaaat tcacaactag 360
tggatcccc gggtgcagc aattcgatat caagcttatc gataccgtcg acctcgaggg 420
ggggcccggt acccaattcg ccctatagtg agtcgta 457

<210> 307
<211> 491
<212> DNA
<213> Homo sapiens

<400> 307
gtgcttggac ggaacccggc gctcgttccc cccccggcc ggccgccc atccagccct 60
ccgtcacctc ttcaccgcac cctcggactg cccaaggcc cccgcgcgcg ctccagcgcc 120
gcgcagccac cgcgcgcgcc gccgcctctc cttagtgcgc gccatgacga ccgcgtccac 180
ctcgcaggtg cgccagaact accaccagga ctcagaggcc gccatcaacc gccagatcaa 240
cctggagctc tacgcctcct acgtttacct gtccatgtct tactactttg accgcgatga 300
tgtggctttg aagaactttg ccaaatactt tcttcaccaa tctcatgagg agagggaaca 360
tgctgagaaa ctgatgaagc tgcagaacca acgaggtggc cgaatcttcc ttcaggatat 420
caagaaacca gactgtgatg actgggagag cgggctgaat gcaatggagt gtgcattaca 480
tttgaaaaa a 491

<210> 308
<211> 421
<212> DNA
<213> Homo sapiens

<400> 308

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ctcagcgctt cttctttctt ggtttgatcc tgactgctgt catggcgtgc cctctggaga 60
aggccctgga tgtgatggtg tccaccttcc acaagtactc gggcaaagag ggtgacaagt 120
tcaagctcaa caagtcagaa ctaaaggagc tgctgaccgg ggagctgccc agcttcttgg 180
ggaaaaggac agatgaagct gctttccaga agctgatgag caacttggac agcaacaggg 240
acaacgaggt ggacttccaa gactactgtg tcttcctgtc ctgcatcgcc atgatgtgta 300
acgaattctt tgaaggcttc ccagataagc agcccaggaa gaaatgaaaa ctcctctgat 360
gtgggtgggg ggtctgccag ctggggccct cctgtcgccc agtgggcaact ttttttttcc 420
c 421
```

<210> 309
<211> 321
<212> DNA
<213> Homo sapiens

```
<400> 309
accaaatggc ggatgacgcc ggtgcagcgg gggggcccgg gggccctggt ggccctggga 60
tggggaaccg cgggtggcttc cgcggaggtt tcggcagtgg catccggggc cggggtcgcg 120
gccgtggaag gggccggggc cgaaggccgg gagctcgggg aggaaggcc gaggataagg 180
agtggatgcc cgtcaccaag ttgggcccgt ttgtcaagga catgaagatc aagtccctgg 240
aggagatcta tctcttctcc ctgcccatta aggaatcaga gatcattgat ttcttcctgg 300
gggcctctct caaggatgag g 321
```

<210> 310
<211> 381
<212> DNA
<213> Homo sapiens

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<400> 310
ttaaccagcc atattggctc aataaatagc ttccgtaagg agttaatttc cttctagaaa 60
tcagtgccta ttttctctgg aaactcaatt tttaaagtc caattccatc tgaagccaag 120
ctgttgtcat tttcattcgg tgacattctc tcccatgaca cccagaaggg gcagaagaac 180
cacatttttc atttatagat gtttgcattc ttgtatttaa aattattttg aaggggttgc 240
ctcattggat ggcttttttt ttttctctcc agggagaagg ggagaaatgt acttggaaat 300
taatgtatgt ttacatctct ttgcaaattc ctgtacatag agatatattt ttttaagtgtg 360
aatgtaacaa catactgtga a 381
```

<210> 311
<211> 538
<212> DNA
<213> Homo sapiens

```
<400> 311
tttgaattta caccaagaac ttctcaataa aagaaaatca tgaatgctcc acaatttcaa 60
cataccacaa gagaagttaa tttcttaaca ttgtgttcta tgattatttg taagaccttc 120
accaagttct gatattcttt aaagacatag ttcaaaattg cttttgaaaa tctgtattct 180
tgaaaatatc cttgttgtgt attaggtttt taaataccag ctaaaggatt acctcactga 240
gtcatcagta ccctctatt cagctcccca agatgatgtg tttttgctta ccctaagaga 300
ggttttcttc ttatttttag ataattcaag tgcttagata aattatgttt tctttaagtg 360
tttatggtaa actcttttaa agaaaattta atatgttata gctgaatctt tttggtaact 420
ttaaatcttt atcatagact ctgtacatat gttcaaatta gctgcttgcc tgatgtgtgt 480
atcatcggtg ggatgacaga acaaacatat ttatgatcat gaataatgtg ctttgtaa 538
```

<210> 312
<211> 176
<212> DNA
<213> Homo sapiens

<400> 312

ggaggagcag ctgagagata gggtcagtga atgcgggttca gcctgctacc tctcctgtct 60
 tcatagaacc attgccttag aattattgta tgacacgttt tttgttggtt aagctgtaag 120
 gttttgttct ttgtgaacat gggatattttg aggggagggt ggaggagta gggaag 176

<210> 313

<211> 396

<212> DNA

<213> Homo sapiens

<400> 313

ccagcaccgc caggcccttg gggacctggg ttctcagact gccaaagaag ccttgccatc 60
 tggcgctccc atggctcttg caacatctcc ccttcgtttt tgaggggggc atgccggggg 120
 agccaccagc ccctcactgg gttcggagga gagtcaggaa gggccaagca cgacaaagca 180
 gaaacatcgg atttggggaa cgcgtgtcaa tcccttggtc cgcagggtcg ggcgggagag 240
 actgttctgt tccttggtga actgtgttgc tgaaagacta cctcgttctt gtcttgatgt 300
 gtcaccgggg caactgcctg ggggcgggga tgggggcagg gtggaagcgg ctccccattt 360
 tataccaaag gtgctacatc tatgtgatgg gtgggg 396

<210> 314

<211> 311

<212> DNA

<213> Homo sapiens

<400> 314

cctcaacatc ctgagagagg actggaagcc agtccttacg ataaactcca taatttatgg 60
 cctgcagtat ctcttcttgg agcccaacc caggagacca ctgaacaagg aggccgcaga 120
 ggtcctgcag aacaaccggc ggctgtttga gcagaacgtg cagcgctcca tgcgggggtg 180
 ctacatgggc tccacctact ttgagcgctg cctgaaatag ggttggcgca taccaccccc 240
 cgccacggcc acaagccctg gcatcccctg caaatattta ttggggggcca tgggtagggg 300
 tttggggggc g 311

<210> 315

<211> 336

<212> DNA

<213> Homo sapiens

<400> 315

tttagaacat ggttatcatc caagactact ctaccctgca acattgaact cccaagagca 60
 aatccacatt cctcttgagt tctgcagctt ctgtgtaaat agggcagctg tcgtctatgc 120
 cgtagaatca catgatctga ggaccattca tggaagctgc taaatagcct agtctgggga 180
 gtcttccata aagttttgca tggagcaaac aaacaggatt aaactagggt tggttccttc 240
 agccctctaa aagcataggg cttagcctgc aggttcctt gggctttctc tgtgtgtgta 300
 gttttgtaaa cactatagca tctgttaaga tccagt 336

<210> 316

<211> 436

<212> DNA

<213> Homo sapiens

<400> 316

aacatggtct gcgtgcctta agagagacgc ttcctgcaga acaggacctg actacaaaga 60
 atgtttccat tgggaattgt ggtaaagact tggagtgtac aatctatgat gatgatgatg 120
 tgtctccatt cctggaaggt cttgaagaaa gaccacagag aaaggcacag cctgctcaac 180
 ctgctgatga acctgcagaa aaggctgatg aaccaatgga acattaagtg ataagccagt 240
 ctatatatgt attatcaaat atgtaagaat acaggcacca catactgatg acaataatct 300
 atactttgaa ccaaaagttg cagagtgggt gaatgctatg ttttaggaat cagtccagat 360
 gtgagttttt tccaagcaac ctactgaaa cctatataat ggaatacatt tttctttgaa 420
 agggctctgta taatca 436

<210> 317
<211> 196
<212> DNA
<213> Homo sapiens

<400> 317
tattccttgt gaagatgata tactatTTTT gttaagcgtg tctgtattta tgtgtgagga 60
gctgctggct tgcagtgcgc gtgcacgtgg agagctggcg cccggagatt ggacggcctg 120
atgctccctc cctgcccctg gtccaggga gctggccgag ggtcctggct cctgaggggc 180
atctgcccct ccccca 196

<210> 318
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 8, 9, 102, 122, 167, 182, 193, 235, 253, 265, 266, 290, 321,
378
<223> n = A,T,C or G

<400> 318
gacgcttngg ccgtaacgat gatcggagac atcctgctgt tcgggacgtt gctgatgaat 60
gccggggcgg tgctgaactt taagctgaaa aagaaggaca cncagggctt tggggaggag 120
tncagggagc ccaacacagg tgacaacatc cggaattctt tgctgancct cagatacttt 180
cnaatcttca tcncctgtg gaacatcttc atgatgttct gcatgattgt gctgntcggc 240
tcttgaatcc cancgatgaa accannaact cactttcccg ggatgccgan tctccattcc 300
tccattcctg atgaattcaa naatgttttt gaccaaaaaa ccgacaacct tcccagaaag 360
tccaagctcg tgggtggngg a 381

<210> 319
<211> 506
<212> DNA
<213> Homo sapiens

<400> 319
ctaagcttta cgaatggggg gacaacttat gataaaaaact agagctagtg aattagccta 60
tttgtaaata cctttgttat aattgatagg atacatcttg gacatggaat tgttaagcca 120
cctctgagca gtgtatgtca ggacttggtc attaggttgg cagcagaggg gcagaaggaa 180
ttatacaggt agagatgtat gcagatgtgt ccatatatgt ccatatttac attttgatag 240
ccattgatgt atgcatctct tggctgtact ataagaacac attaatcaaa tggaaatata 300
ctttgctaata attttaattg tatagatctg ctaatgaatt ctcttaaaaa catactgtat 360
tctgttgctg tgtgtttcat tttaaattga gcattaaggg aatgcagcat ttaaatcaga 420
actctgccaa tgcttttatc tagaggcgtg ttgccatttt tgtcttatat gaaatttctg 480
tccaagaaa ggcaggatta catctt 506

<210> 320
<211> 351
<212> DNA
<213> Homo sapiens

<400> 320
ctgacctgca ggacgaaacc atgaagagcc tgatccttct tgccatcctg gccgccttag 60
cggtagtaac tttgtgttat gaatcacatg aaagcatgga atcttatgaa cttaatccct 120
tcattaacag gagaaatgca aataccttca tatccctca gcagagatgg agagctaaag 180
tccaagagag gatccgagaa cgctctaagc ctgtccacga gctcaatagg gaagcctgtg 240

atgactacag acttttgcga cgctacgcca tggtttatgg atacaatgct gcctataatc 300
gctacttcag gaagcgccga gggaccaa at gagactgagg gaagaaaaa a 351

<210> 321

<211> 421

<212> DNA

<213> Homo sapiens

<400> 321

ctcggaggcg ttcagctgct tcaagatgaa gctgaacatc tccttcccag ccaactggctg 60
ccagaaactc attgaagtgg acgatgaacg caaacttcgt actttctatg agaagcgat 120
ggccacagaa gttgctgctg acgctctggg tgaagaatgg aagggttatg tgggccgaat 180
cagtggtggg aacgacaaac aagggttccc catgaagcag ggtgtcttga cccatggccg 240
tgtccgcctg ctactgagta aggggcattc ctgttacaga ccaaggagaa ctggagaaaag 300
aaagagaaaa tcagttcgtg gttgcattgt ggatgcaaat ctgagcgttc tcaacttggg 360
tattgtaaaa aaaggagaga aggatattcc tggactgact gatactacag tgcctcgccg 420
c 421

<210> 322

<211> 521

<212> DNA

<213> Homo sapiens

<400> 322

agcagctctc ctgccacagc tcctcaccac ctgaaaatgt tcgcctgctc caagtttgtc 60
tccaactccct ccttggtcaa gacacactca cagctgctga gccgtccgct atctgcagt 120
gtgctgaaac gaccggagat actgacagat gagagcctca gcagcttggc agtctcatgt 180
ccccttacct cacttgtctc tagccgcagc ttccaaacca gcgccatttc aaggacatc 240
gacacagcag ccaagttcat tggagctggg gctgccacag ttgggggtggc tggttctggg 300
gctgggattg gaactgtgtt tgggagcctc atcattggtt atgccaggaa cccttctctg 360
aagcaacagc tcttctccta cgccattctg ggctttgccc tctcgaggc catggggctc 420
ttttgtctga tggtagcctt tctcctcctc tttgccatgt gaaggagccg tctccacctc 480
ccatagttct cccgcgtctg gttggccccg tgtgttctt t 521

<210> 323

<211> 435

<212> DNA

<213> Homo sapiens

<400> 323

ccgagggtcg acgcgtgaga cttctccgcc gcagacgccg ccgcgatgag ctacgtcgcc 60
tcctacctgc tggctgccct agggggcaac tcctcccca gcgccaagga catcaagaag 120
atcttggaac gcgtgggtat cgaggcggac gacgaccggc tcaacaagg tcatcagtga 180
ctgaatggaa aaaacattga agacgtcatt gccacgggta ttggcaagct tgccagtga 240
cctgctgggt gggctgtagc cgtctctgct gccccaggct ctgcagcccc tgcgtctggt 300
tctgcccctg ctgcagcaga ggagaagaaa gatgagaaga aggaggagtc tgaagagtca 360
gatgatgaca tgggatttgg cttttttgat taaattcctg ctcccctgca aataaagcct 420
ttttacacat ctcaa 435

<210> 324

<211> 521

<212> DNA

<213> Homo sapiens

<400> 324

aggagatcga ctttcggtgc ccgcaagacc agggctggaa cgccgagatc acgctgcaga 60
tgggtcgagta caagaatcgt caggccatcc tggcgggtcaa atccacgcgg cagaagcagc 120
agcacctggt ccagcagcag cccccctcgc agccgcagcc gcagccgcag ctccagcccc 180

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aaccacagcc tcagcctcag ccgcaacccc agccccaatc acaaccccag cctcagcccc 240
aaccacagcc tcagccccag cagctccacc cgtatccgca tccacatcca catccacact 300
ctcatcctca ctgcacacca caccctcacc cgcaccgca tccgcaccaa ataccgcacc 360
cacacccaca gccgcactcg cagccgcacg gccaccggct tctccgcagc acctccaact 420
ctgcctgaaa ggggcagctc ccgggcaaga caaggttttg aggacttgag gaagtgggac 480
gagcacattt ctattgtctt cacttgatc aaaagcaaaa c 521

```

<210> 325

<211> 451

<212> DNA

<213> Homo sapiens

<400> 325

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attttcattt ccattaacct ggaagctttc atgaatatc tcttctttta aaacatttta 60
acattattta aacagaaaaa gatgggctct ttctggttag ttgttacatg atagcagaga 120
tatttttact tagattactt tgggaatgag agattgttgt cttgaactct ggcaactgtac 180
agtgaatgtg tctgtagttg tgttagtttg cattaagcat gtataacatt caagtatgtc 240
atccaaataa gaggcataata cattgaattg tttttaatcc tctgacaagt tgactcttcg 300
acccccaccc ccacccaaga cattttaata gtaaatagag agagagagaa gagttaatga 360
acatgaggta gtgttcactt ggcaggatga cttttcaata gctcaaatca atttcagtgc 420
ctttatcact tgaattatta acttaatttg a 451

```

<210> 326

<211> 421

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 296

<223> n = A,T,C or G

<400> 326

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cgcggtcgta agggctgagg atttttgggtc cgcacgctcc tgctcctgac tcaccgctgt 60
tcgctctcgc cgaggaacaa gtcggtcagg aagcccgcgc gcaacagcca tggcttttaa 120
ggataccgga aaaacacccg tggagccgga ggtggcaatt caccgaattc gaatcacctt 180
aacaagccgc aacgtaaaat ccttggaata ggtgtgtgct gacttgataa gaggcgcaaa 240
agaaaagaat ctcaaagtga aaggaccagt tcgaatgcct accaagactt tgagantcac 300
tacaagaaaa actccttgtg gtgaagggtc taagacgtgg gatcggtttc agatgagaat 360
tcacaagcga ctcatcgact tgcacagtcc ttctgagatt gttaagcaga ttacttccat 420
c 421

```

<210> 327

<211> 456

<212> DNA

<213> Homo sapiens

<400> 327

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atcttgacga ggctgcgggtg tctgctgcta ttctccgagc ttcgcaatgc cgcctaagga 60
cgacaagaag aagaaggacg ctggaaagtc ggccaagaaa gacaaagacc cagtgaacaa 120
atccgggggc aaggccaaaa agaagaagtg gtccaaaggc aaagtccggg acaagctcaa 180
taacttagtc ttgtttgaca aagctaccta tgataaactc tgtaagggaag ttcccaacta 240
taaacttata accccagctg tggctctcta gagactgaag attcgaggct ccctggccag 300
ggcagccctt caggagctcc ttagtaaaag acttatcaaa ctggtttcaa agcacagagc 360
tcaagtaatt tacaccagaa ataccaaggg tggagatgct ccagctgctg gtgaagatgc 420
atgaataggt ccaaccagct gtacatttgg aaaaaa 456

```

<210> 328

<211> 471
<212> DNA
<213> Homo sapiens

<400> 328
gtggaagtga catcgtcttt aaacctgcg tggcaatccc tgacgcaccg ccgtgatgcc 60
caggggaagac agggcgacct ggaagtccaa ctacttcctt aagatcatcc aactattgga 120
tgattatccg aaatgtttca ttgtgggagc agacaatgtg ggctccaagc agatgcagca 180
gatccgcatg tcccttcgcg ggaaggctgt ggtgctgatg ggcaagaaca ccatgatgcy 240
caaggccatc cgagggcacc tggaaaacaa cccagctctg gagaaactgc tgcctcatat 300
ccgggggaat gtgggctttg tgttcaccaa ggaggacctc actgagatca gggacatggt 360
gctggccaat aagggtgccag ctgctgcccg tgctggtgcc attgccccat gtgaagtcac 420
tgtgccagcc cagaacactg gtctcgggcc cgagaagacc tcctttttcc a 471

<210> 329
<211> 278
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 154, 204
<223> n = A,T,C or G

<400> 329
gtttaaactt aagcttggtg ccgagctcgg atccactagt ccagtgtggt ggaattctag 60
aaattgagat gcccccccag gccagcaaat gttccttttt gttcaaagtc tatttttatt 120
ccttgatatt tttctttttt tttttttttt ttgnggatgg ggacttgtga atttttctaa 180
aggtgctatt taacatggga gganagcgtg tgcggctcca gccagccccg ctgctcactt 240
tccacctctc ctccacctgc ctctggcttc tcaggcct 278

<210> 330
<211> 338
<212> DNA
<213> Homo sapiens

<400> 330
ctcaggcttc aacatcgaat acgcccagc ccccttcgcc ctattcttca tagccgaata 60
cacaacattt attataataa acaccctcac cactacaatc ttcctaggaa caacatatga 120
cgcactctcc cctgaactct acacaacata ttttgtcacc aagaccctac ttctaacctc 180
cctgttctta tgaattcgaa cagcatatcc ccgattccgc tacgaccaac tcatacacct 240
cctatgaaaa aacttcctac cactcaccct agcattactt atatgatatg tctccatacc 300
cattacaatc tccagcattc cccctcaaac ctaaaaaa 338

<210> 331
<211> 2820
<212> DNA
<213> Homo sapiens

<400> 331
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gttgtacctg gaaaacaatg cccagactca atttagtgag ccacagtaca cgaacctggg 120
gctcctgaac agcatggacc agcagattcg gaacggctcc tegtccacca gtccctataa 180
cacagaccac gcgcagaaca gcgtcacgyc gccctcgccc tacgcacagc ccagccccac 240
cttcgatgct ctctctccat caccgcgccat cccctccaac accgactacc caggcccgca 300
cagttccgac gtgtccttcc agcagtcgag caccgccaag tcggccacct ggacgtattc 360
cactgaactg aagaaactct actgccaaat tgcaaagaca tgccccatcc agatcaaggt 420
gatgacccca cctcctcagg gagctgttat ccgcgccatg cctgtctaca aaaaagctga 480

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gcacgtcacg gaggtggtga agcgggtgcc caaccatgag ctgagccgtg agttcaacga 540
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tgtagaagat cccatcacag gaagacagag tgtgctggtta ccttatgagc caccacaggt 660
tggcactgaa ttcacgacag tcttgtacaa tttcatgtgt aacagcagtt gtgttgagg 720
gatgaaccgc cgtccaattt taatcattgt tactctgga accagagatg ggcaagtcct 780
gggccgacgc tgctttgagg cccggtctg tgcttgccca ggaagagaca ggaaggcgga 840
tgaagatagc atcagaaagc agcaagtTtc ggacagtaca aagaacggtg atggtacgaa 900
gcgcccgttt cgtcagaaca cacatggtat ccagatgaca tccatcaaga aacgaagatc 960
cccagatgat gaactgttat acttaccagt gaggggccgt gagacttatg aaatgctgtt 1020
gaagatcaaa gagtccctgg aactcatgca gtaccttcc cagcacaca ttgaaacgta 1080
caggcaacag caacagcagc agcaccagca cttacttcag aaacagacct caatacagtc 1140
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gccttctgtg agccagctta tcaacctca gcagcgcaac gccctcactc ctacaacat 1260
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gttgggctgt tcatcatgtc tggactattt cacgacccag gggctgacca ccatctatca 1500
gattgagcat tactccatgg atgatctggc aagtctgaaa atccctgagc aatttcgaca 1560
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<212> DNA

<213> Homo sapiens

<400> 332

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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gtaaggggta aaaggatagt aagcatagaa accactagaa agtgggctta atggagtct 4440
tgtggcctca gctcaatgca gttagctgaa gaattgaaaa gttttgtttt ggagacgttt 4500
ataaacagaa atggaaagca gagttttcat taaatccttt tacctttttt ttttcttggt 4560
aatcccctaa aataacagta tgtgggatat tgaatgttaa agggatattt ttttctatt 4620
atttttataa ttgtacaaaa ttaagcaaat gttaaaagt ttatatgctt tattaatgtt 4680
ttcaaaaggt attatacatg tgatacattt ttttaagcttc agttgcttgt cttctggtac 4740
tttctgttat gggcttttgg ggagccagaa gccaatctac aatctctttt tgtttgccag 4800
gacatgcaat aaaattttaa aaataaataa aaactaatta agaaataaa 4849

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<210> 336

<211> 1386

<212> DNA

<213> Homo sapiens

<400> 336

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atgttgtacc tggaaaacaa tgcccagact caatttagtg agccacagta cacgaacctg 60
gggtcctcga acagcatgga ccagcagatt cagaacggct cctcgctccac cagtccctat 120
aacacagacc acgcgcagaa cagcgtcacg gcgccctcgc cctacgcaca gccagctcc 180
accttcgatg ctctctctcc atcaccgccc atcccctcca acaccgacta cccaggcccg 240
cacagtttcg acgtgtcctt ccagcagtcg agcaccgcca agtcggccac ctggacgtat 300
tccactgaac tgaagaaact ctactgccaa attgcaaaga catgccccat ccagatcaag 360
gtgatgacct caccctctca gggagctgtt atccgcgcca tgcctgtcta caaaaaagct 420
gagcacgtca cggaggttgt gaagcgtgac cccaaccatg agctgagccg tgaattcaac 480
gagggacaga ttgccctcct tagtcatttg attcgagtag aggggaacag ccatgccag 540
tatgtagaag atcccatcac aggaagacag agtgtgcttg taccttatga gccacccag 600
gttggcactg aattcacgac agtcttgtag aatttcatgt gtaacagcag ttgtgttga 660
gggatgaacc gccgtccaat ttaaatcatt gttactctgg aaaccagaga tgggcaagtc 720
ctgggcccac gctgctttga ggcccggatc tgtgcttgcc caggaaagaga cagggaaggc 780
gatgaagata gcatcagaaa gcagcaagtt tcggacagta caaagaacgg tgatggtacg 840

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aagcgcccggt ttctgcagaa cacacatggt atccagatga catccatcaa gaaacgaaga 900
tccccagatg atgaactgtt atacttacca gtgagggggcc gtgagactta tgaaatgctg 960
ttgaagatca aagagtcctt ggaactcatg cagtaccttc ctcagcacac aattgaaacg 1020
tacaggcaac agcaacagca gcagcaccag cacttacttc agaaacagac ctcaatacag 1080
tctccatctt catatggtaa cagctcccca cctctgaaca aaatgaacag catgaacaag 1140
ctgccttctg tgagccagct tatcaacct cagcagcgca acgcccctcac tcctacaacc 1200
attcctgatg gcatggggagc caacattccc atgatgggca cccacatgcc aatggctgga 1260
gacatgaatg gactcagccc caccagga ctcctcccc cactctccat gccatccacc 1320
tcccactgca cccccacc tocgtatccc acagattgca gcattgtcag gatctggcaa 1380
gtctga 1386

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<210> 337

<211> 1551

<212> DNA

<213> Homo sapiens

<400> 337

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atgtcccaga gcacacagac aaatgaattc ctcagtccag aggttttcca gcatactctgg 60
gattttctgg aacagcctat atgttcagtt cagcccattg acttgaactt tgtggatgaa 120
ccatcagaag atggtgcgac aaacaagatt gagattagca tggactgtat ccgcatgcag 180
gactcggaac tgagtgcacc catgtggcca cagtacacga acctggggct cctgaacagc 240
atggaccagc agattcagaa cggctcctcg tccaccagtc cctataacac agaccacgcg 300
cagaacagcg tcacggcgcc ctgcacctac gcacagcca gctccacctt cgatgctctc 360
tctccatcac ccgccatccc ctccaacacc gactaccacag gcccgcacag tttcgacgtg 420
tccttccagc agtcgagcac cgccaagtcg gccacctgga cgtattccac tgaactgaag 480
aaactctact gccaaattgc aaagacatgc cccatccaga tcaagggtgat gacccacct 540
cctcagggag ctgttatccg cgccatgcct gtctacaaaa aagctgagca cgtcacggag 600
gtggtgaagc ggtgccccaa ccatgagctg agccgtgaat tcaacgaggg acagattgcc 660
cctcctagtc atttgattcg agtagagggg aacagccatg cccagtatgt agaagatccc 720
atcacaggaa gacagagtggt gctggtacct tatgagccac ccaggttgg cactgaattc 780
acgacagtct tgtacaattt catgtgtaac agcagttgtg ttggagggat gaaccgccgt 840
ccaattttaa tcattgttac tctggaaacc agagatgggc aagtccctggg ccgacgctgc 900
tttgaggccc ggatctgtgc ttgcccagga agagacagga aggcggatga agatagcatc 960
agaaagcagc aagtttcgga cagtacaaag aacggtgatg gtacgaagcg cccgtttcgt 1020
cagaacacac atggtatcca gatgacatcc atcaagaaac gaagatcccc agatgatgaa 1080
ctgttatact taccagtgag gggccgtgag acttatgaaa tgctgttgaa gatcaaagag 1140
tccttggaac tcatgcagta ccttctcag cacacaattg aaacgtacag gcaacagcaa 1200
cagcagcagc accagcactt acttcagaaa cagacctcaa tacagtctcc atcttcatat 1260
ggtaacagct cccacctct gaacaaaatg aacagcatga acaagctgcc ttctgtgagc 1320
cagcttatca accctcagca gcgcaacgcc ctcactccta caaccattcc tgatggcatg 1380
ggagccaaca ttcccatgat gggcaccac atgccaatgg ctggagacat gaatggactc 1440
agccccaccc aggcactccc tccccactc tccatgccat ccacctcca ctgcacaccc 1500
ccacctcgt atcccacaga ttgcagcatt gtcaggatct ggcaagtctg a 1551

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<210> 338

<211> 586

<212> PRT

<213> Homo sapiens

<400> 338

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Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
1          5          10         15
Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Arg Asn
20         25         30
Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
35         40         45
Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Pro Thr Phe Asp Ala
50         55         60

```

Leu	Ser	Pro	Ser	Pro	Ala	Ile	Pro	Ser	Asn	Thr	Asp	Tyr	Pro	Gly	Pro
65					70					75					80
His	Ser	Ser	Asp	Val	Ser	Phe	Gln	Gln	Ser	Ser	Thr	Ala	Lys	Ser	Ala
			85						90					95	
Thr	Trp	Thr	Tyr	Ser	Thr	Glu	Leu	Lys	Lys	Leu	Tyr	Cys	Gln	Ile	Ala
			100					105					110		
Lys	Thr	Cys	Pro	Ile	Gln	Ile	Lys	Val	Met	Thr	Pro	Pro	Pro	Gln	Gly
		115					120					125			
Ala	Val	Ile	Arg	Ala	Met	Pro	Val	Tyr	Lys	Lys	Ala	Glu	His	Val	Thr
	130						135				140				
Glu	Val	Val	Lys	Arg	Cys	Pro	Asn	His	Glu	Leu	Ser	Arg	Glu	Phe	Asn
145					150					155					160
Glu	Gly	Gln	Ile	Ala	Pro	Pro	Ser	His	Leu	Ile	Arg	Val	Glu	Gly	Asn
				165					170					175	
Ser	His	Ala	Gln	Tyr	Val	Glu	Asp	Pro	Ile	Thr	Gly	Arg	Gln	Ser	Val
			180					185					190		
Leu	Val	Pro	Tyr	Glu	Pro	Pro	Gln	Val	Gly	Thr	Glu	Phe	Thr	Thr	Val
		195					200					205			
Leu	Tyr	Asn	Phe	Met	Cys	Asn	Ser	Ser	Cys	Val	Gly	Gly	Met	Asn	Arg
	210					215					220				
Arg	Pro	Ile	Leu	Ile	Ile	Val	Thr	Leu	Glu	Thr	Arg	Asp	Gly	Gln	Val
225					230					235					240
Leu	Gly	Arg	Arg	Cys	Phe	Glu	Ala	Arg	Ile	Cys	Ala	Cys	Pro	Gly	Arg
				245					250					255	
Asp	Arg	Lys	Ala	Asp	Glu	Asp	Ser	Ile	Arg	Lys	Gln	Gln	Val	Ser	Asp
			260					265					270		
Ser	Thr	Lys	Asn	Gly	Asp	Gly	Thr	Lys	Arg	Pro	Phe	Arg	Gln	Asn	Thr
		275					280					285			
His	Gly	Ile	Gln	Met	Thr	Ser	Ile	Lys	Lys	Arg	Arg	Ser	Pro	Asp	Asp
	290					295					300				
Glu	Leu	Leu	Tyr	Leu	Pro	Val	Arg	Gly	Arg	Glu	Thr	Tyr	Glu	Met	Leu
305					310					315					320
Leu	Lys	Ile	Lys	Glu	Ser	Leu	Glu	Leu	Met	Gln	Tyr	Leu	Pro	Gln	His
				325					330					335	
Thr	Ile	Glu	Thr	Tyr	Arg	Gln	Gln	Gln	Gln	Gln	Gln	His	Gln	His	Leu
			340					345					350		
Leu	Gln	Lys	Gln	Thr	Ser	Ile	Gln	Ser	Pro	Ser	Ser	Tyr	Gly	Asn	Ser
		355					360					365			
Ser	Pro	Pro	Leu	Asn	Lys	Met	Asn	Ser	Met	Asn	Lys	Leu	Pro	Ser	Val
		370				375					380				
Ser	Gln	Leu	Ile	Asn	Pro	Gln	Gln	Arg	Asn	Ala	Leu	Thr	Pro	Thr	Thr
385					390					395					400
Ile	Pro	Asp	Gly	Met	Gly	Ala	Asn	Ile	Pro	Met	Met	Gly	Thr	His	Met
				405					410					415	
Pro	Met	Ala	Gly	Asp	Met	Asn	Gly	Leu	Ser	Pro	Thr	Gln	Ala	Leu	Pro
			420					425					430		
Pro	Pro	Leu	Ser	Met	Pro	Ser	Thr	Ser	His	Cys	Thr	Pro	Pro	Pro	Pro
		435					440					445			
Tyr	Pro	Thr	Asp	Cys	Ser	Ile	Val	Ser	Phe	Leu	Ala	Arg	Leu	Gly	Cys
	450					455					460				
Ser	Ser	Cys	Leu	Asp	Tyr	Phe	Thr	Thr	Gln	Gly	Leu	Thr	Thr	Ile	Tyr
465					470					475					480
Gln	Ile	Glu	His	Tyr	Ser	Met	Asp	Asp	Leu	Ala	Ser	Leu	Lys	Ile	Pro
				485					490					495	
Glu	Gln	Phe	Arg	His	Ala	Ile	Trp	Lys	Gly	Ile	Leu	Asp	His	Arg	Gln
			500					505					510		
Leu	His	Glu	Phe	Ser	Ser	Pro	Ser	His	Leu	Leu	Arg	Thr	Pro	Ser	Ser
		515					520					525			

Ala Ser Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val
 530 535 540
 Ile Asp Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro
 545 550 555 560
 Arg Asp Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn
 565 570 575
 Lys Gln Gln Arg Ile Lys Glu Glu Gly Glu
 580 585

<210> 339
 <211> 641
 <212> PRT
 <213> Homo sapiens

<400> 339
 Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
 1 5 10 15
 Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
 20 25 30
 Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
 35 40 45
 Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
 50 55 60
 Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Glu Leu Leu Asn Ser
 65 70 75 80
 Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
 85 90 95
 Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
 100 105 110
 Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
 115 120 125
 Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
 130 135 140
 Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
 145 150 155 160
 Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
 165 170 175
 Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
 180 185 190
 Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
 195 200 205
 Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
 210 215 220
 Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
 225 230 235 240
 Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
 245 250 255
 Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
 260 265 270
 Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
 275 280 285
 Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
 290 295 300
 Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
 305 310 315 320
 Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
 325 330 335

Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
 340 345 350
 Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
 355 360 365
 Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
 370 375 380
 Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
 385 390 395 400
 Gln Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser
 405 410 415
 Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser
 420 425 430
 Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg
 435 440 445
 Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile
 450 455 460
 Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu
 465 470 475 480
 Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser
 485 490 495
 His Cys Thr Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Gly
 500 505 510
 Phe Leu Ala Arg Leu Gly Cys Ser Ser Cys Leu Asp Tyr Phe Thr Thr
 515 520 525
 Gln Gly Leu Thr Thr Ile Tyr Gln Ile Glu His Tyr Ser Met Asp Asp
 530 535 540
 Leu Ala Ser Leu Lys Ile Pro Glu Gln Phe Arg His Ala Ile Trp Lys
 545 550 555 560
 Gly Ile Leu Asp His Arg Gln Leu His Glu Phe Ser Ser Pro Ser His
 565 570 575
 Leu Leu Arg Thr Pro Ser Ser Ala Ser Thr Val Ser Val Gly Ser Ser
 580 585 590
 Glu Thr Arg Gly Glu Arg Val Ile Asp Ala Val Arg Phe Thr Leu Arg
 595 600 605
 Gln Thr Ile Ser Phe Pro Pro Arg Asp Glu Trp Asn Asp Phe Asn Phe
 610 615 620
 Asp Met Asp Ala Arg Arg Asn Lys Gln Gln Arg Ile Lys Glu Glu Gly
 625 630 635 640
 Glu

<210> 340

<211> 448

<212> PRT

<213> Homo sapiens

<400> 340

Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
 1 5 10 15
 Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
 20 25 30
 Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
 35 40 45
 Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
 50 55 60
 Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser
 65 70 75 80

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Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
      85                      90                      95
Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
      100                    105                    110
Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
      115                    120                    125
Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
      130                    135                    140
Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
      145                    150                    155                    160
Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
      165                    170                    175
Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
      180                    185                    190
Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
      195                    200                    205
Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
      210                    215                    220
Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
      225                    230                    235                    240
Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
      245                    250                    255
Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
      260                    265                    270
Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
      275                    280                    285
Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
      290                    295                    300
Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
      305                    310                    315                    320
Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
      325                    330                    335
Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
      340                    345                    350
Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
      355                    360                    365
Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
      370                    375                    380
Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
      385                    390                    395                    400
Gln Gln Gln His Gln His Leu Leu Gln Lys His Leu Leu Ser Ala Cys
      405                    410                    415
Phe Arg Asn Glu Leu Val Glu Pro Arg Arg Glu Thr Pro Lys Gln Ser
      420                    425                    430
Asp Val Phe Phe Arg His Ser Lys Pro Pro Asn Arg Ser Val Tyr Pro
      435                    440                    445

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<210> 341

<211> 356

<212> PRT

<213> Homo sapiens

<400> 341

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Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
  1              5              10              15
Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
      20              25              30

```

Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
 35 40 45
 Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
 50 55 60
 Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
 65 70 75 80
 His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
 85 90 95
 Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
 100 105 110
 Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
 115 120 125
 Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
 130 135 140
 Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
 145 150 155 160
 Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
 165 170 175
 Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
 180 185 190
 Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val
 195 200 205
 Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg
 210 215 220
 Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
 225 230 235 240
 Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg
 245 250 255
 Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
 260 265 270
 Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Ser Arg Gln Asn Thr
 275 280 285
 His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
 290 295 300
 Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
 305 310 315 320
 Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
 325 330 335
 Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu
 340 345 350
 Leu Gln Lys Gln
 355

<210> 342

<211> 680

<212> PRT

<213> Homo sapiens

<400> 342

Met Asn Phe Glu Thr Ser Arg Cys Ala Thr Leu Gln Tyr Cys Pro Asp
 1 5 10 15
 Pro Tyr Ile Gln Arg Phe Val Glu Thr Pro Ala His Phe Ser Trp Lys
 20 25 30
 Glu Ser Tyr Tyr Arg Ser Thr Met Ser Gln Ser Thr Gln Thr Asn Glu
 35 40 45
 Phe Leu Ser Pro Glu Val Phe Gln His Ile Trp Asp Phe Leu Glu Gln
 50 55 60

Pro Ile Cys Ser Val Gln Pro Ile Asp Leu Asn Phe Val Asp Glu Pro
 65 70 75 80
 Ser Glu Asp Gly Ala Thr Asn Lys Ile Glu Ile Ser Met Asp Cys Ile
 85 90 95
 Arg Met Gln Asp Ser Asp Leu Ser Asp Pro Met Trp Pro Gln Tyr Thr
 100 105 110
 Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn Gly Ser
 115 120 125
 Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser Val Thr
 130 135 140
 Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala Leu Ser
 145 150 155 160
 Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro His Ser
 165 170 175
 Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala Thr Trp
 180 185 190
 Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala Lys Thr
 195 200 205
 Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly Ala Val
 210 215 220
 Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr Glu Val
 225 230 235 240
 Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn Glu Gly
 245 250 255
 Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn Ser His
 260 265 270
 Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val Leu Val
 275 280 285
 Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val Leu Tyr
 290 295 300
 Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg Arg Pro
 305 310 315 320
 Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val Leu Gly
 325 330 335
 Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg Asp Arg
 340 345 350
 Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp Ser Thr
 355 360 365
 Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr His Gly
 370 375 380
 Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp Glu Leu
 385 390 395 400
 Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu Leu Lys
 405 410 415
 Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His Thr Ile
 420 425 430
 Glu Thr Tyr Arg Gln Gln Gln Gln Gln His Gln His Leu Leu Gln
 435 440 445
 Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser Ser Pro
 450 455 460
 Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val Ser Gln
 465 470 475 480
 Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr Ile Pro
 485 490 495
 Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met Pro Met
 500 505 510
 Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro Pro Pro
 515 520 525

Leu Ser Met Pro Ser Thr Ser Gln Cys Thr Pro Pro Pro Pro Tyr Pro
 530 535 540
 Thr Asp Cys Ser Ile Val Ser Phe Leu Ala Arg Leu Gly Cys Ser Ser
 545 550 555 560
 Cys Leu Asp Tyr Phe Thr Thr Gln Gly Leu Thr Thr Ile Tyr Gln Ile
 565 570 575
 Glu His Tyr Ser Met Asp Asp Leu Ala Ser Leu Lys Ile Pro Glu Gln
 580 585 590
 Phe Arg His Ala Ile Trp Lys Gly Ile Leu Asp His Arg Gln Leu His
 595 600 605
 Glu Phe Ser Ser Pro Ser His Leu Leu Arg Thr Pro Ser Ser Ala Ser
 610 615 620
 Thr Val Ser Val Gly Ser Ser Glu Thr Arg Gly Glu Arg Val Ile Asp
 625 630 635 640
 Ala Val Arg Phe Thr Leu Arg Gln Thr Ile Ser Phe Pro Pro Arg Asp
 645 650 655
 Glu Trp Asn Asp Phe Asn Phe Asp Met Asp Ala Arg Arg Asn Lys Gln
 660 665 670
 Gln Arg Ile Lys Glu Glu Gly Glu
 675 680

<210> 343

<211> 461

<212> PRT

<213> Homo sapiens

<400> 343

Met Leu Tyr Leu Glu Asn Asn Ala Gln Thr Gln Phe Ser Glu Pro Gln
 1 5 10 15
 Tyr Thr Asn Leu Gly Leu Leu Asn Ser Met Asp Gln Gln Ile Gln Asn
 20 25 30
 Gly Ser Ser Ser Thr Ser Pro Tyr Asn Thr Asp His Ala Gln Asn Ser
 35 40 45
 Val Thr Ala Pro Ser Pro Tyr Ala Gln Pro Ser Ser Thr Phe Asp Ala
 50 55 60
 Leu Ser Pro Ser Pro Ala Ile Pro Ser Asn Thr Asp Tyr Pro Gly Pro
 65 70 75 80
 His Ser Phe Asp Val Ser Phe Gln Gln Ser Ser Thr Ala Lys Ser Ala
 85 90 95
 Thr Trp Thr Tyr Ser Thr Glu Leu Lys Lys Leu Tyr Cys Gln Ile Ala
 100 105 110
 Lys Thr Cys Pro Ile Gln Ile Lys Val Met Thr Pro Pro Pro Gln Gly
 115 120 125
 Ala Val Ile Arg Ala Met Pro Val Tyr Lys Lys Ala Glu His Val Thr
 130 135 140
 Glu Val Val Lys Arg Cys Pro Asn His Glu Leu Ser Arg Glu Phe Asn
 145 150 155 160
 Glu Gly Gln Ile Ala Pro Pro Ser His Leu Ile Arg Val Glu Gly Asn
 165 170 175
 Ser His Ala Gln Tyr Val Glu Asp Pro Ile Thr Gly Arg Gln Ser Val
 180 185 190
 Leu Val Pro Tyr Glu Pro Pro Gln Val Gly Thr Glu Phe Thr Thr Val
 195 200 205
 Leu Tyr Asn Phe Met Cys Asn Ser Ser Cys Val Gly Gly Met Asn Arg
 210 215 220
 Arg Pro Ile Leu Ile Ile Val Thr Leu Glu Thr Arg Asp Gly Gln Val
 225 230 235 240

Leu Gly Arg Arg Cys Phe Glu Ala Arg Ile Cys Ala Cys Pro Gly Arg
 245 250 255
 Asp Arg Lys Ala Asp Glu Asp Ser Ile Arg Lys Gln Gln Val Ser Asp
 260 265 270
 Ser Thr Lys Asn Gly Asp Gly Thr Lys Arg Pro Phe Arg Gln Asn Thr
 275 280 285
 His Gly Ile Gln Met Thr Ser Ile Lys Lys Arg Arg Ser Pro Asp Asp
 290 295 300
 Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu Thr Tyr Glu Met Leu
 305 310 315 320
 Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln Tyr Leu Pro Gln His
 325 330 335
 Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln Gln His Gln His Leu
 340 345 350
 Leu Gln Lys Gln Thr Ser Ile Gln Ser Pro Ser Ser Tyr Gly Asn Ser
 355 360 365
 Ser Pro Pro Leu Asn Lys Met Asn Ser Met Asn Lys Leu Pro Ser Val
 370 375 380
 Ser Gln Leu Ile Asn Pro Gln Gln Arg Asn Ala Leu Thr Pro Thr Thr
 385 390 395 400
 Ile Pro Asp Gly Met Gly Ala Asn Ile Pro Met Met Gly Thr His Met
 405 410 415
 Pro Met Ala Gly Asp Met Asn Gly Leu Ser Pro Thr Gln Ala Leu Pro
 420 425 430
 Pro Pro Leu Ser Met Pro Ser Thr Ser His Cys Thr Pro Pro Pro Pro
 435 440 445
 Tyr Pro Thr Asp Cys Ser Ile Val Arg Ile Trp Gln Val
 450 455 460

<210> 344

<211> 516

<212> PRT

<213> Homo sapiens

<400> 344

Met Ser Gln Ser Thr Gln Thr Asn Glu Phe Leu Ser Pro Glu Val Phe
 1 5 10 15
 Gln His Ile Trp Asp Phe Leu Glu Gln Pro Ile Cys Ser Val Gln Pro
 20 25 30
 Ile Asp Leu Asn Phe Val Asp Glu Pro Ser Glu Asp Gly Ala Thr Asn
 35 40 45
 Lys Ile Glu Ile Ser Met Asp Cys Ile Arg Met Gln Asp Ser Asp Leu
 50 55 60
 Ser Asp Pro Met Trp Pro Gln Tyr Thr Asn Leu Gly Leu Leu Asn Ser
 65 70 75 80
 Met Asp Gln Gln Ile Gln Asn Gly Ser Ser Ser Thr Ser Pro Tyr Asn
 85 90 95
 Thr Asp His Ala Gln Asn Ser Val Thr Ala Pro Ser Pro Tyr Ala Gln
 100 105 110
 Pro Ser Ser Thr Phe Asp Ala Leu Ser Pro Ser Pro Ala Ile Pro Ser
 115 120 125
 Asn Thr Asp Tyr Pro Gly Pro His Ser Phe Asp Val Ser Phe Gln Gln
 130 135 140
 Ser Ser Thr Ala Lys Ser Ala Thr Trp Thr Tyr Ser Thr Glu Leu Lys
 145 150 155 160
 Lys Leu Tyr Cys Gln Ile Ala Lys Thr Cys Pro Ile Gln Ile Lys Val
 165 170 175

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Met Thr Pro Pro Pro Gln Gly Ala Val Ile Arg Ala Met Pro Val Tyr
      180      185      190
Lys Lys Ala Glu His Val Thr Glu Val Val Lys Arg Cys Pro Asn His
      195      200      205
Glu Leu Ser Arg Glu Phe Asn Glu Gly Gln Ile Ala Pro Pro Ser His
      210      215      220
Leu Ile Arg Val Glu Gly Asn Ser His Ala Gln Tyr Val Glu Asp Pro
      225      230      235      240
Ile Thr Gly Arg Gln Ser Val Leu Val Pro Tyr Glu Pro Pro Gln Val
      245      250      255
Gly Thr Glu Phe Thr Thr Val Leu Tyr Asn Phe Met Cys Asn Ser Ser
      260      265      270
Cys Val Gly Gly Met Asn Arg Arg Pro Ile Leu Ile Ile Val Thr Leu
      275      280      285
Glu Thr Arg Asp Gly Gln Val Leu Gly Arg Arg Cys Phe Glu Ala Arg
      290      295      300
Ile Cys Ala Cys Pro Gly Arg Asp Arg Lys Ala Asp Glu Asp Ser Ile
      305      310      315      320
Arg Lys Gln Gln Val Ser Asp Ser Thr Lys Asn Gly Asp Gly Thr Lys
      325      330      335
Arg Pro Phe Arg Gln Asn Thr His Gly Ile Gln Met Thr Ser Ile Lys
      340      345      350
Lys Arg Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly
      355      360      365
Arg Glu Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu
      370      375      380
Met Gln Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln
      385      390      395      400
Gln Gln Gln His Gln His Leu Leu Gln Lys Gln Thr Ser Ile Gln Ser
      405      410      415
Pro Ser Ser Tyr Gly Asn Ser Ser Pro Pro Leu Asn Lys Met Asn Ser
      420      425      430
Met Asn Lys Leu Pro Ser Val Ser Gln Leu Ile Asn Pro Gln Gln Arg
      435      440      445
Asn Ala Leu Thr Pro Thr Thr Ile Pro Asp Gly Met Gly Ala Asn Ile
      450      455      460
Pro Met Met Gly Thr His Met Pro Met Ala Gly Asp Met Asn Gly Leu
      465      470      475      480
Ser Pro Thr Gln Ala Leu Pro Pro Pro Leu Ser Met Pro Ser Thr Ser
      485      490      495
His Cys Thr Pro Pro Pro Tyr Pro Thr Asp Cys Ser Ile Val Arg
      500      505      510
Ile Trp Gln Val
      515

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<210> 345

<211> 1800

<212> DNA

<213> Homo sapiens

<400> 345

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gcgcctcatt gccactgcag tgactaaagc tgggaagacg ctggtcagtt cacctgcccc 60
actggttggt ttttaaaca attctgatac aggcgacatc ctactgacc gagcaaagat 120
tgacattcgt atcatcactg tgcaccattg gcttctaggc actccagtgg ggtaggagaa 180
ggaggtctga aacctcgca gagggatctt gccctcattc tttgggtctg aaactgggc 240
agtcgttgga aacaggactc agggataaac cagcgcaatg gattggggga cgctgcacac 300
tttcatcggg ggtgtcaaca aacctccac cagcatcggg aaggtgtgga tcacagtcac 360

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ctttattttt cgagtcata tccatgtggt ggctgccag gaagtgtggg gtgacgagca 420
agaggacttc gtctgcaaca cactgcaacc gggatgcaaa aatgtgtgct atgaccactt 480
tttcccggtg tccacatcc ggctgtgggc cctccagctg atcttcgtct ccaccccagc 540
gctgctgggt gccatgcatg tggcctacta caggcacgaa accactcgca agttcaggcg 600
aggagagaag aggaatgatt tcaaagacat agaggacatt aaaaagcaca aggttcggat 660
agagggggtc ctgtgggtga cgtacaccag cagcatcttt ttccgaatca tctttgaagc 720
agcctttatg tatgtgtttt acttccttta caatgggtac cacctgccct gggtgttgaa 780
atgtgggatt gaccctgcc ccaaccttgt tgactgcttt atttctaggc caacagagaa 840
gaccgtgttt accattttta tgatttctgc gtctgtgatt tgcattgctg ttaacgtggc 900
agagtgtgtc tacctgctgc tgaaagtgtg ttttaggaga tcaaagagag cacagacgca 960
aaaaaatcac cccaatcatg ccctaaagga gagtaagcag aatgaaatga atgagctgat 1020
ttcagatagt ggtcaaaatg caatcacagg tttcccaagc taaacatttc aaggtaaaat 1080
gtagctgcgt cataaggaga cttctgtctt ctccagaagg caataccaac ctgaaagtgc 1140
cttctgtagc ctgaagagtt tgtaaatgac tttcataata aatagacact tgagttaact 1200
ttttgtagga tacttgctcc attcatacac aacgtaatca aatatgtggg ccatctctga 1260
aaacaagaga ctgcttgaca aaggagcatt gcagtcactt tgacaggttc cttttaagtg 1320
gactctctga caaagtgggt actttctgaa aatttatata actgttgttg ataaggaaca 1380
tttatccagg aattgatacg tttattagga aaagatattt ttataggctt ggatgttttt 1440
agttccgact ttgaatttat ataaagtatt tttataatga ctggctcttc ttacctggaa 1500
aaacatgcga tgtagtattt agaattacac cacaagtatc taaatttcca acttacaaga 1560
ggtcctatct tgtaaatatt gttttgcatt gtctgttggc aaatttgtga actgtcatga 1620
tacgcttaag gtgggaaagt gttcattgca caatatattt ttactgcttt ctgaatgtag 1680
acggaacagt gtggaagcag aaggcttttt taactcatcc gtttgccga tcgttgacga 1740
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<210> 346

<211> 261

<212> PRT

<213> Homo sapiens

<400> 346

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Met Asp Trp Gly Thr Leu His Thr Phe Ile Gly Gly Val Asn Lys His
1          5          10          15
Ser Thr Ser Ile Gly Lys Val Trp Ile Thr Val Ile Phe Ile Phe Arg
          20          25          30
Val Met Ile Leu Val Val Ala Ala Gln Glu Val Trp Gly Asp Glu Gln
          35          40          45
Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
50          55          60
Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
65          70          75          80
Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
          85          90          95
Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg
100          105          110
Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys His Lys Val Arg Ile
115          120          125
Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile
130          135          140
Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly
145          150          155          160
Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn
          165          170          175
Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
180          185          190
Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
195          200          205

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Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg
 210 215 220
 Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys
 225 230 235 240
 Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile
 245 250 255
 Thr Gly Phe Pro Ser
 260

<210> 347
 <211> 1740
 <212> DNA
 <213> Homo sapiens

<400> 347
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 atcttcaagg acgccaagat cccggtgtcg ggacccttcc tggatgaagac tggctacgag 120
 ttcgtggact gcccgagcga gagctgggcc ctcaaggcca tcgaggcgct ttcaggtaaa 180
 atagaactgc acgggaaacc catagaagtt gagcactcgg tcccaaaaag gcaaaggatt 240
 cggaacttc agatacgaat tatcccgct catttacagt gggagggtgct ggatagttaa 300
 ctagtccagt atggagtggg ggagagctgt gagcaagtga acactgactc ggaaactgca 360
 gttgtaaatg taacctattc cagtaaggac caagctagac aagcactaga caaactgaat 420
 ggatttcagt tagagaattt caccttgaaa gtacgctata tccctgatga aacggccgcc 480
 cagcaaaacc ccttgacgca gccccgaggt cgccgggggc ttgggcagag gggctcctca 540
 aggcagggtt ctccaggatc cgtatccaag cagaaaccat gtgatttgcc tctgcgctg 600
 ctggttccca cccaatttgt tggagccatc ataggaaaag aaggtgccac cattcggaac 660
 atcaccacac agaccagtc taaaatcgat gtccaccgta aagaaaatgc gggggctgct 720
 gagaagtcga ttactatcct ctctactcct gaaggcacct ctgcggcttg taagtctatt 780
 ctggagatta tgataagga agctcaagat ataaaattca cagaagagat ccccttgaag 840
 attttagctc ataataactt tgttggacgt cttattggtg aagaagggaag aaatcttaaa 900
 aaaattgagc aagacacaga cactaaaatc acgatatctc cattgcagga attgacgctg 960
 tataatccag aacgcactat tacagttaaa ggcaatgttg agacatgtgc caaagctgag 1020
 gaggagatca tgaagaaaat cagggtgtct tatgaaaatg atattgcttc tatgaatctt 1080
 caagcacatt taattcctgg attaaatctg aacgccttgg gtctgttccc acccacttca 1140
 gggatgccac ctccacactc agggccccc tccagccatga ctctcccta cccgcagttt 1200
 gagcaatcag aaacggagac tgttcactct tttatcccag ctctatcagt cgggtgccatc 1260
 atcggcaagc agggccagca catcaagcag ctttctcgct ttgtgggagc ttcaattaag 1320
 attgctccag cggaagcacc agatgttaaa gtgaggatgg tgattatcac tggaccacca 1380
 gaggctcagt tcaaggctca gggagaagatt tatggaaaaa ttaaagaaga aaactttgtt 1440
 agtccataag aagagggtgaa acttgaagct catatcagag tgccatcctt tgctgctggc 1500
 agagttattg gaaaaggagg caaaacgggtg aatgaacttc agaatttgtc aagtgcagaa 1560
 gttgtgtgoc ctctgacca gacacctgat gagaatgacc aagtgggtgt caaaataact 1620
 ggtcacttct atgcttgcca gggtgcccag agaaaaatc aggaattct gactcaggta 1680
 aagcagcacc aacaacagaa ggctctgcaa agtgaccac ctgagtcag acggaagtaa 1740

<210> 348
 <211> 579
 <212> PRT
 <213> Homo sapiens

<400> 348
 Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
 1 5 10 15
 Asp Leu Glu Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro
 20 25 30
 Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser

500 505 510
 Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr
 515 520 525
 Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr
 530 535 540
 Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val
 545 550 555 560
 Lys Gln His Gln Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser
 565 570 575
 Arg Arg Lys

<210> 349
 <211> 207
 <212> DNA
 <213> Homo sapiens

<400> 349
 atgtggcagc ccctcttctt caagtggctc ttgtcctgtt gccctgggag ttctcaaatt 60
 gctgcagcag cctccaccca gcctgaggat gacatcaata cacagaggaa gaagagtcag 120
 gaaaagatga gagaagttac agactctcct gggcgacccc gagagcttac cattcctcag 180
 acttcttcac atggtgctaa cagattt 207

<210> 350
 <211> 69
 <212> PRT
 <213> Homo sapiens

<400> 350
 Met Trp Gln Pro Leu Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly
 1 5 10 15
 Ser Ser Gln Ile Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp Ile
 20 25 30
 Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp
 35 40 45
 Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His
 50 55 60
 Gly Ala Asn Arg Phe
 65

<210> 351
 <211> 1012
 <212> DNA
 <213> Homo sapiens

<400> 351
 ccctctagaa ataattttgt ttaactttaa gaaggagata tacatatgca tcaccatcac 60
 catcacacgg ccgcgtccga taacttccag ctgtcccagg gtgggcaggg attcgccatt 120
 ccgatcgggc aggcgatggc gatcgcgggc cagatcaagc ttcccaccgt tcatatcggg 180
 cctaccgcct tcctcggcctt ggggtgtgtc gacaacaacg gcaacggcgc acgagtccaa 240
 cgcggtggtcg ggagcgctcc ggcggaagt ctcggcatct ccaccggcga cgtgatcacc 300
 gcggtcgacg gcgtccgat caactcggcc accgcgatgg cggacgcgct taacgggcat 360
 catcccggtg acgtcatctc ggtgacctgg caaaccaagt cgggcggcac gcgtacaggg 420
 aacgtgacat tggccgaggg acccccggcc gaattcatgg attgggggac gctgcacact 480
 ttcatcgggg gtgtcaacaa acactccacc agcatcggga aggtgtggat cacagtcac 540
 tttattttcc gagtcatgat cctcgtggtg gctgcccagg aagtgtgggg tgacgagcaa 600

gaggacttcg tctgcaacac actgcaaccg ggatgcaaaa atgtgtgcta tgaccacttt 660
 ttcccgggtgt cccacatccg gctgtggggcc ctccagctga tcttcgtctc caccaccagcg 720
 ctgctggtgg ccatgcatgt ggcctactac aggcacgaaa ccactcgcaa gttcaggcga 780
 ggagagaaga ggaatgattt caaagacata gaggacatta aaaagcagaa ggttcggata 840
 gaggggtgac tcgagcacca ccaccaccac cactgagatc cggctgctaa caaagcccga 900
 aaggaagctg agttggctgc tgccaccgct gagcaataac tagcataacc ccttggggcc 960
 tctaaacggg tcttgagggg tttttgctg aaaggaggaa ctatatccgg at 1012

<210> 352

<211> 267

<212> PRT

<213> Homo sapiens

<400> 352

Met His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
 1 5 10 15
 Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
 20 25 30
 Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
 35 40 45
 Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
 50 55 60
 Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
 65 70 75 80
 Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
 85 90 95
 Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
 100 105 110
 Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
 115 120 125
 Leu Ala Glu Gly Pro Pro Ala Glu Phe Met Asp Trp Gly Thr Leu His
 130 135 140
 Thr Phe Ile Gly Gly Val Asn Lys His Ser Thr Ser Ile Gly Lys Val
 145 150 155 160
 Trp Ile Thr Val Ile Phe Ile Phe Arg Val Met Ile Leu Val Val Ala
 165 170 175
 Ala Gln Glu Val Trp Gly Asp Glu Gln Glu Asp Phe Val Cys Asn Thr
 180 185 190
 Leu Gln Pro Gly Cys Lys Asn Val Cys Tyr Asp His Phe Phe Pro Val
 195 200 205
 Ser His Ile Arg Leu Trp Ala Leu Gln Leu Ile Phe Val Ser Thr Pro
 210 215 220
 Ala Leu Leu Val Ala Met His Val Ala Tyr Tyr Arg His Glu Thr Thr
 225 230 235 240
 Arg Lys Phe Arg Arg Gly Glu Lys Arg Asn Asp Phe Lys Asp Ile Glu
 245 250 255
 Asp Ile Lys Lys Gln Lys Val Arg Ile Glu Gly
 260 265

<210> 353

<211> 900

<212> DNA

<213> Homo sapiens

<400> 353

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 cagggtattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

accgttcata tcgggcctac cgccttcctc ggcttggtg ttgtcgacaa caacggcaac 180
 ggcgacagag tccaacgcgt ggtcgggagc gctcggcg caagtctcgg catctccacc 240
 ggcgacgtga tcaccgcggt cgacggcgct cggatcaact cggccaccgc gatggcggac 300
 gcgcttaacg ggcatcatcc cggtgacgtc atctcgggtga cctggcaaac caagtcgggc 360
 ggacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt ccacgaaacc 420
 actcgcaagt tcaggcgagg agagaagagg aatgatttca aagacataga ggacattaaa 480
 aagcagaagg ttcgataga ggggtcgctg tgggtggacgt acaccagcag catctttttc 540
 cgaatcatct ttgaagcagc ctttatgtat gtgttttact tcctttacaa tgggtaccac 600
 ctgccctggg tgttgaatg tgggattgac cctgcccaca accttggtga ctgctttatt 660
 tctaggccaa cagagaagac cgtgtttacc atttttatga tttctgcgtc tgtgatttgc 720
 atgctgctta acgtggcaga gttgtgctac ctgctgctga aagtgtgttt taggagatca 780
 aagagagcac agacgcaaaa aaatcacccc aatcatgccc taaaggagag taagcagaat 840
 gaaatgaatg agctgatttc agatagtgtt caaatgcaa tcacagggtt cccaagctaa 900

<210> 354

<211> 299

<212> PRT

<213> Homo sapiens

<400> 354

Met	His	His	His	His	His	His	Thr	Ala	Ala	Ser	Asp	Asn	Phe	Gln	Leu
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Ser	Gln	Gly	Gly	Gln	Gly	Phe	Ala	Ile	Pro	Ile	Gly	Gln	Ala	Met	Ala
		20						25					30		
Ile	Ala	Gly	Gln	Ile	Lys	Leu	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala
		35					40					45			
Phe	Leu	Gly	Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val
	50					55				60					
Gln	Arg	Val	Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr
	65				70					75				80	
Gly	Asp	Val	Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr
			85						90					95	
Ala	Met	Ala	Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser
		100					105						110		
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	His	Glu	Thr	Thr	Arg	Lys	Phe
	130					135					140				
Arg	Arg	Gly	Glu	Lys	Arg	Asn	Asp	Phe	Lys	Asp	Ile	Glu	Asp	Ile	Lys
	145			150					155					160	
Lys	Gln	Lys	Val	Arg	Ile	Glu	Gly	Ser	Leu	Trp	Trp	Thr	Tyr	Thr	Ser
			165					170						175	
Ser	Ile	Phe	Phe	Arg	Ile	Ile	Phe	Glu	Ala	Ala	Phe	Met	Tyr	Val	Phe
		180					185						190		
Tyr	Phe	Leu	Tyr	Asn	Gly	Tyr	His	Leu	Pro	Trp	Val	Leu	Lys	Cys	Gly
	195					200					205				
Ile	Asp	Pro	Cys	Pro	Asn	Leu	Val	Asp	Cys	Phe	Ile	Ser	Arg	Pro	Thr
	210				215						220				
Glu	Lys	Thr	Val	Phe	Thr	Ile	Phe	Met	Ile	Ser	Ala	Ser	Val	Ile	Cys
	225				230					235					240
Met	Leu	Leu	Asn	Val	Ala	Glu	Leu	Cys	Tyr	Leu	Leu	Leu	Lys	Val	Cys
			245						250					255	
Phe	Arg	Arg	Ser	Lys	Arg	Ala	Gln	Thr	Gln	Lys	Asn	His	Pro	Asn	His
		260					265						270		
Ala	Leu	Lys	Glu	Ser	Lys	Gln	Asn	Glu	Met	Asn	Glu	Leu	Ile	Ser	Asp
	275					280						285			
Ser	Gly	Gln	Asn	Ala	Ile	Thr	Gly	Phe	Pro	Ser					

290

295

<210> 355
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 355
 ggagtacagc ttcaagacaa tggg

24

<210> 356
 <211> 31
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 356
 ccatgggaat tcattataat aattttgttc c

31

<210> 357
 <211> 920
 <212> PRT
 <213> Homo sapiens

<400> 357
 Met Gln His His His His His His Gly Val Gln Leu Gln Asp Asn Gly
 1 5 10 15
 Tyr Asn Gly Leu Leu Ile Ala Ile Asn Pro Gln Val Pro Glu Asn Gln
 20 25 30
 Asn Leu Ile Ser Asn Ile Lys Glu Met Ile Thr Glu Ala Ser Phe Tyr
 35 40 45
 Leu Phe Asn Ala Thr Lys Arg Arg Val Phe Phe Arg Asn Ile Lys Ile
 50 55 60
 Leu Ile Pro Ala Thr Trp Lys Ala Asn Asn Asn Ser Lys Ile Lys Gln
 65 70 75 80
 Glu Ser Tyr Glu Lys Ala Asn Val Ile Val Thr Asp Trp Tyr Gly Ala
 85 90 95
 His Gly Asp Asp Pro Tyr Thr Leu Gln Tyr Arg Gly Cys Gly Lys Glu
 100 105 110
 Gly Lys Tyr Ile His Phe Thr Pro Asn Phe Leu Leu Asn Asp Asn Leu
 115 120 125
 Thr Ala Gly Tyr Gly Ser Arg Gly Arg Val Phe Val His Glu Trp Ala
 130 135 140
 His Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asp Lys Pro Phe
 145 150 155 160
 Tyr Ile Asn Gly Gln Asn Gln Ile Lys Val Thr Arg Cys Ser Ser Asp
 165 170 175
 Ile Thr Gly Ile Phe Val Cys Glu Lys Gly Pro Cys Pro Gln Glu Asn
 180 185 190
 Cys Ile Ile Ser Lys Leu Phe Lys Glu Gly Cys Thr Phe Ile Tyr Asn
 195 200 205
 Ser Thr Gln Asn Ala Thr Ala Ser Ile Met Phe Met Gln Ser Leu Ser

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210          215          220
Ser Val Val Glu Phe Cys Asn Ala Ser Thr His Asn Gln Glu Ala Pro
225          230          235          240
Asn Leu Gln Asn Gln Met Cys Ser Leu Arg Ser Ala Trp Asp Val Ile
          245          250          255
Thr Asp Ser Ala Asp Phe His His Ser Phe Pro Met Asn Gly Thr Glu
          260          265          270
Leu Pro Pro Pro Pro Thr Phe Ser Leu Val Glu Ala Gly Asp Lys Val
          275          280          285
Val Cys Leu Val Leu Asp Val Ser Ser Lys Met Ala Glu Ala Asp Arg
          290          295          300
Leu Leu Gln Leu Gln Gln Ala Ala Glu Phe Tyr Leu Met Gln Ile Val
305          310          315          320
Glu Ile His Thr Phe Val Gly Ile Ala Ser Phe Asp Ser Lys Gly Glu
          325          330          335
Ile Arg Ala Gln Leu His Gln Ile Asn Ser Asn Asp Asp Arg Lys Leu
          340          345          350
Leu Val Ser Tyr Leu Pro Thr Thr Val Ser Ala Lys Thr Asp Ile Ser
          355          360          365
Ile Cys Ser Gly Leu Lys Lys Gly Phe Glu Val Val Glu Lys Leu Asn
          370          375          380
Gly Lys Ala Tyr Gly Ser Val Met Ile Leu Val Thr Ser Gly Asp Asp
385          390          395          400
Lys Leu Leu Gly Asn Cys Leu Pro Thr Val Leu Ser Ser Gly Ser Thr
          405          410          415
Ile His Ser Ile Ala Leu Gly Ser Ser Ala Ala Pro Asn Leu Glu Glu
          420          425          430
Leu Ser Arg Leu Thr Gly Gly Leu Lys Phe Phe Val Pro Asp Ile Ser
          435          440          445
Asn Ser Asn Ser Met Ile Asp Ala Phe Ser Arg Ile Ser Ser Gly Thr
          450          455          460
Gly Asp Ile Phe Gln Gln His Ile Gln Leu Glu Ser Thr Gly Glu Asn
465          470          475          480
Val Lys Pro His His Gln Leu Lys Asn Thr Val Thr Val Asp Asn Thr
          485          490          495
Val Gly Asn Asp Thr Met Phe Leu Val Thr Trp Gln Ala Ser Gly Pro
          500          505          510
Pro Glu Ile Ile Leu Phe Asp Pro Asp Gly Arg Lys Tyr Tyr Thr Asn
          515          520          525
Asn Phe Ile Thr Asn Leu Thr Phe Arg Thr Ala Ser Leu Trp Ile Pro
          530          535          540
Gly Thr Ala Lys Pro Gly His Trp Thr Tyr Thr Leu Asn Asn Thr His
545          550          555          560
His Ser Leu Gln Ala Leu Lys Val Thr Val Thr Ser Arg Ala Ser Asn
          565          570          575
Ser Ala Val Pro Pro Ala Thr Val Glu Ala Phe Val Glu Arg Asp Ser
          580          585          590
Leu His Phe Pro His Pro Val Met Ile Tyr Ala Asn Val Lys Gln Gly
          595          600          605
Phe Tyr Pro Ile Leu Asn Ala Thr Val Thr Ala Thr Val Glu Pro Glu
          610          615          620
Thr Gly Asp Pro Val Thr Leu Arg Leu Leu Asp Asp Gly Ala Gly Ala
625          630          635          640
Asp Val Ile Lys Asn Asp Gly Ile Tyr Ser Arg Tyr Phe Phe Ser Phe
          645          650          655
Ala Ala Asn Gly Arg Tyr Ser Leu Lys Val His Val Asn His Ser Pro
          660          665          670
Ser Ile Ser Thr Pro Ala His Ser Ile Pro Gly Ser His Ala Met Tyr

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675	680	685
Val Pro Gly Tyr Thr Ala Asn Gly Asn Ile Gln Met Asn Ala Pro Arg		
690	695	700
Lys Ser Val Gly Arg Asn Glu Glu Glu Arg Lys Trp Gly Phe Ser Arg		
705	710	715
Val Ser Ser Gly Gly Ser Phe Ser Val Leu Gly Val Pro Ala Gly Pro		
725	730	735
His Pro Asp Val Phe Pro Pro Cys Lys Ile Ile Asp Leu Glu Ala Val		
740	745	750
Lys Val Glu Glu Glu Leu Thr Leu Ser Trp Thr Ala Pro Gly Glu Asp		
755	760	765
Phe Asp Gln Gly Gln Ala Thr Ser Tyr Glu Ile Arg Met Ser Lys Ser		
770	775	780
Leu Gln Asn Ile Gln Asp Asp Phe Asn Asn Ala Ile Leu Val Asn Thr		
785	790	795
Ser Lys Arg Asn Pro Gln Gln Ala Gly Ile Arg Glu Ile Phe Thr Phe		
805	810	815
Ser Pro Gln Ile Ser Thr Asn Gly Pro Glu His Gln Pro Asn Gly Glu		
820	825	830
Thr His Glu Ser His Arg Ile Tyr Val Ala Ile Arg Ala Met Asp Arg		
835	840	845
Asn Ser Leu Gln Ser Ala Val Ser Asn Ile Ala Gln Ala Pro Leu Phe		
850	855	860
Ile Pro Pro Asn Ser Asp Pro Val Pro Ala Arg Asp Tyr Leu Ile Leu		
865	870	875
Lys Gly Val Leu Thr Ala Met Gly Leu Ile Gly Ile Ile Cys Leu Ile		
885	890	895
Ile Val Val Thr His His Thr Leu Ser Arg Lys Lys Arg Ala Asp Lys		
900	905	910
Lys Glu Asn Gly Thr Lys Leu Leu		
915	920	

<210> 358

<211> 2773

<212> DNA

<213> Homo sapiens

<400> 358

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gaaatgataa ctgaagcttc attttaccta tttaatgcta ccaagagaag agtatttttc 180
agaaatataa agattttaat acctgccaca tggaaagcta ataataacag caaaataaaa 240
caagaatcat atgaaaaggc aaatgtcata gtgactgact ggtatggggc acatggagat 300
gatccataca ccctacaata cagagggtgt ggaaaagagg gaaaatacat tcatttcaca 360
cctaatttcc tactgaatga taacttaaca gctggctacg gatcacgagg ccgagtgttt 420
gtccatgaat gggccacact ccgttggggg gtgttcgatg agtataacaa tgacaaacct 480
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atttttgtgt gtgaaaaagg tccttgcccc caagaaaact gtattattag taagcttttt 600
aaagaaggat gcacctttat ctacaatagc acccaaatg caactgcac aataatgttc 660
atgcaaagtt tatcttctgt ggttgaattt tgtaatgcaa gtaccacaa ccaagaagca 720
ccaaacctac agaaccagat gtgcagcttc agaagtgcac gggatgtaat cacagactct 780
gctgactttc accacagctt tcccatgaac gggactgagc ttccacctcc tcccacattc 840
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cagctacacc aaattaacag caatgatgat cgaaagtgtc tggtttcata tctgccacc 1080
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gttgaaaaac tgaatggaaa agcttatggc tctgtgatga tattagtac cagcggagat 1200
gataagcttc ttggcaattg cttacccact gtgctcagca gtggttcaac aattcactcc 1260
attgccctgg gttcatctgc agccccaat ctggaggaat tatcacgtct tacaggaggt 1320
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caggcgctc tgtttattcc ccccaattct gatcctgtac ctgccagaga ttatcttata 2640
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<210> 359

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 359

tggcagcccc tcttcttcaa gtggc

25

<210> 360

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 360

cgccagaatt catcaaacia atctgttagc acc

33

<210> 361

<211> 77

<212> PRT

<213> Homo sapiens

<400> 361

Met Gln His His His His His His Trp Gln Pro Leu Phe Phe Lys Trp

```

      1           5           10           15
Leu Leu Ser Cys Cys Pro Gly Ser Ser Gln Ile Ala Ala Ala Ala Ser
      20           25           30
Thr Gln Pro Glu Asp Asp Ile Asn Thr Gln Arg Lys Lys Ser Gln Glu
      35           40           45
Lys Met Arg Glu Val Thr Asp Ser Pro Gly Arg Pro Arg Glu Leu Thr
      50           55           60
Ile Pro Gln Thr Ser Ser His Gly Ala Asn Arg Phe Val
      65           70           75

```

<210> 362
 <211> 244
 <212> DNA
 <213> Homo sapiens

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<400> 362
catatgcagc atcaccacca tcaccactgg cagcccctct tcttcaagtg gctcttgtcc 60
tggtgccctg ggagttctca aattgctgca gcagcctcca cccagcctga ggatgacatc 120
aatacacaga ggaagaagag tcaggaaaag atgagagaag ttacagactc tcctgggcga 180
ccccgagagc ttaccattcc tcagacttct tcacatgggtg ctaacagatt tgtttgatga 240
attc                                     244

```

<210> 363
 <211> 20
 <212> PRT
 <213> Homo sapiens

```

<400> 363
Met Trp Gln Pro Leu Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly
      1           5           10           15
Ser Ser Gln Ile
      20

```

<210> 364
 <211> 60
 <212> DNA
 <213> Homo sapiens

```

<400> 364
atgtggcagc ccctcttctt caagtggctc ttgtcctgtt gccctgggag ttctcaaatt 60

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<210> 365
 <211> 20
 <212> PRT
 <213> Homo sapiens

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<400> 365
Gly Ser Ser Gln Ile Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp
      1           5           10           15
Ile Asn Thr Gln
      20

```

<210> 366
 <211> 60

<212> DNA
<213> Homo sapiens

<400> 366
gggagttctc aaattgctgc agcagcctcc acccagcctg aggatgacat caatacacag 60

<210> 367
<211> 20
<212> PRT
<213> Homo sapiens

<400> 367
Lys Pro Gly His Trp Thr Tyr Thr Leu Asn Asn Thr His His Ser Leu
1 5 10 15
Gln Ala Leu Lys
20

<210> 368
<211> 2343
<212> DNA
<213> Homo sapiens

<400> 368
attccggagc gtttgcggct tcgcttcatg gccgctctcc cgccccctcc gggatctgtg 60
gggagctggg gagcccgagc cggcccgagg cgggagctgg cgagccgagc ggagacctgt 120
gcgcccgcgc tctgaggcgc agcatgtgaa gcggagacgg catccagtgg ggggagagcc 180
tctcagccgg ccgggatggc taccacggcc gagctcttcg aggagccttt tgtggcagat 240
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gcttttgatc ctaaaagatt attagaagaa tttgtaaatc atattcagga actccagata 360
atggatgaaa ggattcagag gaaagtagag aaactagagc aacaatgtca gaaagaagcc 420
aaggaatttg ccaagaaggt acaagagctg cagaaaagca atcagggtgc cttccaacat 480
ttccaagaac tagatgagca cattagctat gttagcaacta aagtctgtca ccttggagac 540
cagttagagg gggtaaaccac acccagacaa cgggcagtgagg aggtcagaa attgatgaaa 600
tactttaatg agtttctaga tggagaattg aaatctgatg tttttacaaa ttctgaaaag 660
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gatagatttt cagaagttaa atccaaaatt gcaagtaaat accatgattt agaatgccag 780
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aagaaaaacag attttaagcc agaagatgaa aacaatgttt tgattcaata tactaatgcc 1920
tgtgtaaaaa tctgtgctta cgtaagaaaa caagtggaga agattaaaaa ttccatggat 1980

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gggaagaatg tggatacagt ttgatggaa cttggagtag gttttcatcg acttatctat 2040
gagcatcttc aacaatattc ctacagttgt atgggtggca tgggtggccat ttgtgatgta 2100
gccgaatata ggaagtgtgc caaagacttc aagattccaa tgggtattaca tctttttgat 2160
actctgcatg ctctttgcaa tcttctggta gttgccccag ataatttaaa gcaagtctgc 2220
tcaggagAAC aacttgctaa tctggacaag aatatacttc actccttcgt acaacttcgt 2280
gctgattata gatctgcccg ccttgctcga cacttcagct gagattgaat ttacaaagga 2340
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<210> 369

<211> 708

<212> PRT

<213> Homo sapiens

<400> 369

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Tyr Ile Glu Arg Leu Val Trp Arg Thr Pro Gly Gly Gly Ser Arg Gly
20 25 30
Gly Pro Glu Ala Phe Asp Pro Lys Arg Leu Leu Glu Glu Phe Val Asn
35 40 45
His Ile Gln Glu Leu Gln Ile Met Asp Glu Arg Ile Gln Arg Lys Val
50 55 60
Glu Lys Leu Glu Gln Gln Cys Gln Lys Glu Ala Lys Glu Phe Ala Lys
65 70 75 80
Lys Val Gln Glu Leu Gln Lys Ser Asn Gln Val Ala Phe Gln His Phe
85 90 95
Gln Glu Leu Asp Glu His Ile Ser Tyr Val Ala Thr Lys Val Cys His
100 105 110
Leu Gly Asp Gln Leu Glu Gly Val Asn Thr Pro Arg Gln Arg Ala Val
115 120 125
Glu Ala Gln Lys Leu Met Lys Tyr Phe Asn Glu Phe Leu Asp Gly Glu
130 135 140
Leu Lys Ser Asp Val Phe Thr Asn Ser Glu Lys Ile Lys Glu Ala Ala
145 150 155 160
Asp Ile Ile Gln Lys Leu His Leu Ile Ala Gln Glu Leu Pro Phe Asp
165 170 175
Arg Phe Ser Glu Val Lys Ser Lys Ile Ala Ser Lys Tyr His Asp Leu
180 185 190
Glu Cys Gln Leu Ile Gln Glu Phe Thr Ser Ala Gln Arg Arg Gly Glu
195 200 205
Ile Ser Arg Met Arg Glu Val Ala Ala Val Leu Leu His Phe Lys Gly
210 215 220
Tyr Ser His Cys Val Asp Val Tyr Ile Lys Gln Cys Gln Glu Gly Ala
225 230 235 240
Tyr Leu Arg Asn Asp Ile Phe Glu Asp Ala Gly Ile Leu Cys Gln Arg
245 250 255
Val Asn Lys Gln Val Gly Asp Ile Phe Ser Asn Pro Glu Thr Val Leu
260 265 270
Ala Lys Leu Ile Gln Asn Val Phe Glu Ile Lys Leu Gln Ser Phe Val
275 280 285
Lys Glu Gln Leu Glu Glu Cys Arg Lys Ser Asp Ala Glu Gln Tyr Leu
290 295 300
Lys Asn Leu Tyr Asp Leu Tyr Thr Arg Thr Thr Asn Leu Ser Ser Lys
305 310 315 320
Leu Met Glu Phe Asn Leu Gly Thr Asp Lys Gln Thr Phe Leu Ser Lys
325 330 335
Leu Ile Lys Ser Ile Phe Ile Ser Tyr Leu Glu Asn Tyr Ile Glu Val
340 345 350

```


Glu Thr Gly Tyr Leu Lys Ser Arg Ser Ala Met Ile Leu Gln Arg Tyr
 355 360 365
 Tyr Asp Ser Lys Asn His Gln Lys Arg Ser Ile Gly Thr Gly Gly Ile
 370 375 380
 Gln Asp Leu Lys Glu Arg Ile Arg Gln Arg Thr Asn Leu Pro Leu Gly
 385 390 395 400
 Pro Ser Ile Asp Thr His Gly Glu Thr Phe Leu Ser Gln Glu Val Val
 405 410 415
 Val Asn Leu Leu Gln Glu Thr Lys Gln Ala Phe Glu Arg Cys His Arg
 420 425 430
 Leu Ser Asp Pro Ser Asp Leu Pro Arg Asn Ala Phe Arg Ile Phe Thr
 435 440 445
 Ile Leu Val Glu Phe Leu Cys Ile Glu His Ile Asp Tyr Ala Leu Glu
 450 455 460
 Thr Gly Leu Ala Gly Ile Pro Ser Ser Asp Ser Arg Asn Ala Asn Leu
 465 470 475 480
 Tyr Phe Leu Asp Val Val Gln Gln Ala Asn Thr Ile Phe His Leu Phe
 485 490 495
 Asp Lys Gln Phe Asn Asp His Leu Met Pro Leu Ile Ser Ser Ser Pro
 500 505 510
 Lys Leu Ser Glu Cys Leu Gln Lys Lys Lys Glu Ile Ile Glu Gln Met
 515 520 525
 Glu Met Lys Leu Asp Thr Gly Ile Asp Arg Thr Leu Asn Cys Met Ile
 530 535 540
 Gly Gln Met Lys His Ile Leu Ala Ala Glu Gln Lys Lys Thr Asp Phe
 545 550 555 560
 Lys Pro Glu Asp Glu Asn Asn Val Leu Ile Gln Tyr Thr Asn Ala Cys
 565 570 575
 Val Lys Val Cys Ala Tyr Val Arg Lys Gln Val Glu Lys Ile Lys Asn
 580 585 590
 Ser Met Asp Gly Lys Asn Val Asp Thr Val Leu Met Glu Leu Gly Val
 595 600 605
 Arg Phe His Arg Leu Ile Tyr Glu His Leu Gln Gln Tyr Ser Tyr Ser
 610 615 620
 Cys Met Gly Gly Met Leu Ala Ile Cys Asp Val Ala Glu Tyr Arg Lys
 625 630 635 640
 Cys Ala Lys Asp Phe Lys Ile Pro Met Val Leu His Leu Phe Asp Thr
 645 650 655
 Leu His Ala Leu Cys Asn Leu Leu Val Val Ala Pro Asp Asn Leu Lys
 660 665 670
 Gln Val Cys Ser Gly Glu Gln Leu Ala Asn Leu Asp Lys Asn Ile Leu
 675 680 685
 His Ser Phe Val Gln Leu Arg Ala Asp Tyr Arg Ser Ala Arg Leu Ala
 690 695 700
 Arg His Phe Ser
 705

<210> 370

<211> 60

<212> DNA

<213> Homo sapiens

<400> 370

gtcaatcact ctcccagcat aagcaccocca gccactcta ttccaggag tcatgctatg 60

<210> 371

<211> 60
<212> DNA
<213> Homo sapiens

<400> 371
agtagaattt cctctggaac tggagacatt ttccagcaac atattcagct tgaaagtaca 60

<210> 372
<211> 60
<212> DNA
<213> Homo sapiens

<400> 372
ccagagactg gagatcctgt tacgctgaga ctcccttgatg atggagcagg tgctgatgtt 60

<210> 373
<211> 60
<212> DNA
<213> Homo sapiens

<400> 373
ttacagtctg ctgtatctaa cattgccagc ggcctctgt ttattcccc caattctgat 60

<210> 374
<211> 60
<212> DNA
<213> Homo sapiens

<400> 374
gctgtgcccc cagccactgt ggaagccttt gtggaaagag acagcctcca tttcctcat 60

<210> 375
<211> 60
<212> DNA
<213> Homo sapiens

<400> 375
aaaaacacag tgactgtgga taatactgtg ggcaacgaca ctatgtttct agttacgtgg 60

<210> 376
<211> 20
<212> PRT
<213> Homo sapiens

<400> 376
Leu Gln Ser Ala Val Ser Asn Ile Ala Gln Ala Pro Leu Phe Ile Pro
1 5 10 15
Pro Asn Ser Asp
20

<210> 377
<211> 20

Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile Pro Gly
1 5 10 15
Ser His Ala Met
20

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<210> 378
<211> 20
<212> PRT
<213> Homo sapiens
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Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu Leu Asp Asp Gly Ala
1 5 10 15
Gly Ala Asp Val
20

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<210> 379
<211> 20
<212> PRT
<213> Homo sapiens
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Ala Val Pro Pro Ala Thr Val Glu Ala Phe Val Glu Arg Asp Ser Leu
1 5 10 15
His Phe Pro His
20

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<210> 380
<211> 20
<212> PRT
<213> Homo sapiens
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Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
1 5 10 15
Leu Glu Ser Thr
20

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<210> 381
<211> 20
<212> PRT
<213> Homo sapiens
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Lys Asn Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe
1 5 10 15
Leu Val Thr Trp
20

<210> 382
<211> 20
<212> PRT
<213> Homo sapiens

<400> 382
Lys Pro Gly His Trp Thr Tyr Thr Leu Asn Asn Thr His His Ser Leu
1 5 10 15
Gln Ala Leu Lys
20

<210> 383
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 383
cggcgaattc atggattggg ggacgctgc

29

<210> 384
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 384
cggcctcgag tcaccctct atccgaacct tctgc

35

<210> 385
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
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<400> 385
cggcgaattc cacgaaccac tcgcaagttc ag

32

<210> 386
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 386
cggcctcgagt tagcttgggc ctgtgattgc

30

<210> 387
<211> 20

<212> PRT

<213> Homo sapiens

<400> 387

Phe Phe Lys Trp Leu Leu Ser Cys Cys Pro Gly Ser Ser Gln Ile Ala
1 5 10 15
Ala Ala Ala Ser
20

<210> 388

<211> 19

<212> PRT

<213> Homo sapiens

<400> 388

Leu Ser Cys Cys Pro Gly Ser Ser Gln Ile Ala Ala Ala Ser Thr Gln
1 5 10 15
Pro Glu Asp

<210> 389

<211> 20

<212> PRT

<213> Homo sapiens

<400> 389

Ala Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp Ile Asn Thr Gln Arg
1 5 10 15
Lys Lys Ser Gln
20

<210> 390

<211> 20

<212> PRT

<213> Homo sapiens

<400> 390

Thr Gln Pro Glu Asp Asp Ile Asn Thr Gln Arg Lys Lys Ser Gln Glu
1 5 10 15
Lys Met Arg Glu
20

<210> 391

<211> 20

<212> PRT

<213> Homo sapiens

<400> 391

Asp Ile Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val
1 5 10 15
Thr Asp Ser Pro
20

<210> 392
<211> 20
<212> PRT
<213> Homo sapiens

<400> 392
Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp Ser Pro Gly
1 5 10 15
Arg Pro Arg Glu
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<210> 393
<211> 20
<212> PRT
<213> Homo sapiens

<400> 393
Glu Lys Met Arg Glu Val Thr Asp Ser Pro Gly Arg Pro Arg Glu Leu
1 5 10 15
Thr Ile Pro Gln
20

<210> 394
<211> 20
<212> PRT
<213> Homo sapiens

<400> 394
Val Thr Asp Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr
1 5 10 15
Ser Ser His Gly
20

<210> 395
<211> 19
<212> PRT
<213> Homo sapiens

<400> 395
Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His Gly Ala
1 5 10 15
Asn Arg Phe

<210> 396
<211> 19
<212> PRT
<213> Homo sapiens

<400> 396
Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
1 5 10 15
Asp Leu Glu

<210> 397
<211> 20
<212> PRT
<213> Homo sapiens

<400> 397
Ser Glu Asn Ala Ala Pro Ser Asp Leu Glu Ser Ile Phe Lys Asp Ala
1 5 10 15
Lys Ile Pro Val
20

<210> 398
<211> 20
<212> PRT
<213> Homo sapiens

<400> 398
Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro Phe Leu Val
1 5 10 15
Lys Thr Gly Tyr
20

<210> 399
<211> 20
<212> PRT
<213> Homo sapiens

<400> 399
Ser Gly Pro Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro
1 5 10 15
Asp Glu Ser Trp
20

<210> 400
<211> 20
<212> PRT
<213> Homo sapiens

<400> 400
Ala Phe Val Asp Cys Pro Asp Glu Ser Trp Ala Leu Lys Ala Ile Glu
1 5 10 15
Ala Leu Ser Gly
20

<210> 401
<211> 20
<212> PRT
<213> Homo sapiens

<400> 401
Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His Gly
1 5 10 15

Lys Pro Ile Glu
20

<210> 402
<211> 20
<212> PRT
<213> Homo sapiens

<400> 402
Lys Ile Glu Leu His Gly Lys Pro Ile Glu Val Glu His Ser Val Pro
1 5 10 15
Lys Arg Gln Arg
20

<210> 403
<211> 20
<212> PRT
<213> Homo sapiens

<400> 403
Val Glu His Ser Val Pro Lys Arg Gln Arg Ile Arg Lys Leu Gln Ile
1 5 10 15
Arg Asn Ile Pro
20

<210> 404
<211> 20
<212> PRT
<213> Homo sapiens

<400> 404
Ile Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu
1 5 10 15
Val Leu Asp Ser
20

<210> 405
<211> 20
<212> PRT
<213> Homo sapiens

<400> 405
Ala Val Val Asn Val Thr Tyr Ser Ser Lys Asp Gln Ala Arg Gln Ala
1 5 10 15
Leu Asp Lys Leu
20

<210> 406
<211> 20
<212> PRT
<213> Homo sapiens

<400> 406

Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu Glu
1 5 10 15
Asn Phe Thr Leu
20

<210> 407
<211> 20
<212> PRT
<213> Homo sapiens

<400> 407
Asn Gly Phe Gln Leu Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro
1 5 10 15
Asp Glu Thr Ala
20

<210> 408
<211> 20
<212> PRT
<213> Homo sapiens

<400> 408
Lys Val Ala Tyr Ile Pro Asp Glu Thr Ala Ala Gln Gln Asn Pro Leu
1 5 10 15
Gln Gln Pro Arg
20

<210> 409
<211> 20
<212> PRT
<213> Homo sapiens

<400> 409
Ala Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly
1 5 10 15
Gln Arg Gly Ser
20

<210> 410
<211> 20
<212> PRT
<213> Homo sapiens

<400> 410
Gly Arg Arg Gly Leu Gly Gln Arg Gly Ser Ser Arg Gln Gly Ser Pro
1 5 10 15
Gly Ser Val Ser
20

<210> 411
<211> 20
<212> PRT
<213> Homo sapiens

<400> 411

Ser	Arg	Gln	Gly	Ser	Pro	Gly	Ser	Val	Ser	Lys	Gln	Lys	Pro	Cys	Asp
1				5					10					15	
Leu	Pro	Leu	Arg												
				20											

<210> 412

<211> 20

<212> PRT

<213> Homo sapiens

<400> 412

Lys	Gln	Lys	Pro	Cys	Asp	Leu	Pro	Leu	Arg	Leu	Leu	Val	Pro	Thr	Gln
1				5					10					15	
Phe	Val	Gly	Ala												
				20											

<210> 413

<211> 20

<212> PRT

<213> Homo sapiens

<400> 413

Leu	Leu	Val	Pro	Thr	Gln	Phe	Val	Gly	Ala	Ile	Ile	Gly	Lys	Glu	Gly
1				5					10					15	
Ala	Thr	Ile	Arg												
				20											

<210> 414

<211> 20

<212> PRT

<213> Homo sapiens

<400> 414

Ile	Ile	Gly	Lys	Glu	Gly	Ala	Thr	Ile	Arg	Asn	Ile	Thr	Lys	Gln	Thr
1				5					10					15	
Gln	Ser	Lys	Ile												
				20											

<210> 415

<211> 20

<212> PRT

<213> Homo sapiens

<400> 415

Asn	Ile	Thr	Lys	Gln	Thr	Gln	Ser	Lys	Ile	Asp	Val	His	Arg	Lys	Glu
1				5					10					15	
Asn	Ala	Gly	Ala												
				20											

<210> 416

<211> 20

<212> PRT

<213> Homo sapiens

<400> 416

Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala Glu Lys Ser Ile Thr
 1 5 10 15
 Ile Leu Ser Thr
 20

<210> 417

<211> 20

<212> PRT

<213> Homo sapiens

<400> 417

Ala Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala
 1 5 10 15
 Ala Cys Lys Ser
 20

<210> 418

<211> 20

<212> PRT

<213> Homo sapiens

<400> 418

Pro Glu Gly Thr Ser Ala Ala Cys Lys Ser Ile Leu Glu Ile Met His
 1 5 10 15
 Lys Glu Ala Gln
 20

<210> 419

<211> 20

<212> PRT

<213> Homo sapiens

<400> 419

Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys Phe Thr Glu
 1 5 10 15
 Glu Ile Pro Leu
 20

<210> 420

<211> 455

<212> DNA

<213> Homo sapiens

<400> 420

gaagacatgc ttacttcccc ttcaccttcc ttcattgatgt gggaagagtg ctgcaaccca 60
 gccctagcca acgccgcattg agagggagtg tgccgagggc ttctgagaag gtttctctca 120
 catctagaaa gaagcgctta agatgtggca gccctcttc ttcaagtggc tcttgtcctg 180
 ttgccctggg agttctcaaa ttgctgcagc agcctccacc cagcctgagg atgacatcaa 240
 tacacagagg aagaagagtc aggaaaagat gagagaagtt acagactctc ctgggcgacc 300
 ccgagagctt accattcttc agacttcttc acatggtgct aacagatttg ttcctaaaag 360

taaagctcta gaggccgtca aattggcaat agaagccggg ttccaccata ttgattctgc 420
 acatgtttac aataatgagg agcaggttgg actgg 455

<210> 421
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 421
 actagtgtcc gcgtggcggc ctac

24

<210> 422
 <211> 34
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 422
 catgagaatt catcacatgc cttgaaggc tccc

34

<210> 423
 <211> 161
 <212> PRT
 <213> Homo sapiens

<400> 423
 Met Gln His His His His His His Thr Ser Val Arg Val Ala Ala
 1 5 10 15
 Tyr Phe Glu Asn Phe Leu Ala Ala Trp Arg Pro Val Lys Ala Ser Asp
 20 25 30
 Gly Asp Tyr Tyr Thr Leu Ala Val Pro Met Gly Asp Val Pro Met Asp
 35 40 45
 Gly Ile Ser Val Ala Asp Ile Gly Ala Ala Val Ser Ser Ile Phe Asn
 50 55 60
 Ser Pro Glu Glu Phe Leu Gly Lys Ala Val Gly Leu Ser Ala Glu Ala
 65 70 75 80
 Leu Thr Ile Gln Gln Tyr Ala Asp Val Leu Ser Lys Ala Leu Gly Lys
 85 90 95
 Glu Val Arg Asp Ala Lys Ile Thr Pro Glu Ala Phe Glu Lys Leu Gly
 100 105 110
 Phe Pro Ala Ala Lys Glu Ile Ala Asn Met Cys Arg Phe Tyr Glu Met
 115 120 125
 Lys Pro Asp Arg Asp Val Asn Leu Thr His Gln Leu Asn Pro Lys Val
 130 135 140
 Lys Ser Phe Ser Gln Phe Ile Ser Glu Asn Gln Gly Ala Phe Lys Gly
 145 150 155 160
 Met

<210> 424
 <211> 489
 <212> DNA

<213> Homo sapiens

<400> 424

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tttctcgcgg cgtggcgccc cgtgaaagcc tctgatggag attactacac cttggctgta 120
ccgatgggag atgtaccaat ggatggatc tctgttgctg atattggagc agccgtctct 180
agcattttta attctccaga ggaattttta ggcaaggccg tggggctcag tgcagaagca 240
ctaacaatac agcaatatgc tgatgttttg tccaaggctt tggggaaaga agtccgagat 300
gcaaagatta ccccggaagc ttctgagaag ctgggattcc ctgcagcaaa ggaaatagcc 360
aatatgtgtc gtttctatga aatgaagcca gaccgagatg tcaatctcac ccaccaacta 420
aatcccaaaag tcaaaagctt cagccagttt atctcagaga accagggagc cttcaagggc 480
atgtgatga 489
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<210> 425

<211> 32

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 425

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aacaaactgt atatcggaaa cctcagcgag aa 32
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<210> 426

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 426

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ccatagaatt cattacttcc gtcttgactg agg 33
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<210> 427

<211> 586

<212> PRT

<213> Homo sapiens

<400> 427

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Met Gln His His His His His Asn Lys Leu Tyr Ile Gly Asn Leu
 1          5          10          15
Ser Glu Asn Ala Ala Pro Ser Asp Leu Glu Ser Ile Phe Lys Asp Ala
 20          25          30
Lys Ile Pro Val Ser Gly Pro Phe Leu Val Lys Thr Gly Tyr Ala Phe
 35          40          45
Val Asp Cys Pro Asp Glu Ser Trp Ala Leu Lys Ala Ile Glu Ala Leu
 50          55          60
Ser Gly Lys Ile Glu Leu His Gly Lys Pro Ile Glu Val Glu His Ser
 65          70          75          80
Val Pro Lys Arg Gln Arg Ile Arg Lys Leu Gln Ile Arg Asn Ile Pro
 85          90          95
Pro His Leu Gln Trp Glu Val Leu Asp Ser Leu Leu Val Gln Tyr Gly
100          105          110
Val Val Glu Ser Cys Glu Gln Val Asn Thr Asp Ser Glu Thr Ala Val
115          120          125
Val Asn Val Thr Tyr Ser Ser Lys Asp Gln Ala Arg Gln Ala Leu Asp
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130	135	140	
Lys Leu Asn Gly Phe Gln Leu Glu Asn Phe Thr Leu Lys Val Ala Tyr			
145	150	155	160
Ile Pro Asp Glu Thr Ala Ala Gln Gln Asn Pro Leu Gln Gln Pro Arg			
	165	170	175
Gly Arg Arg Gly Leu Gly Gln Arg Gly Ser Ser Arg Gln Gly Ser Pro			
	180	185	190
Gly Ser Val Ser Lys Gln Lys Pro Cys Asp Leu Pro Leu Arg Leu Leu			
	195	200	205
Val Pro Thr Gln Phe Val Gly Ala Ile Ile Gly Lys Glu Gly Ala Thr			
	210	215	220
Ile Arg Asn Ile Thr Lys Gln Thr Gln Ser Lys Ile Asp Val His Arg			
225	230	235	240
Lys Glu Asn Ala Gly Ala Ala Glu Lys Ser Ile Thr Ile Leu Ser Thr			
	245	250	255
Pro Glu Gly Thr Ser Ala Ala Cys Lys Ser Ile Leu Glu Ile Met His			
	260	265	270
Lys Glu Ala Gln Asp Ile Lys Phe Thr Glu Glu Ile Pro Leu Lys Ile			
	275	280	285
Leu Ala His Asn Asn Phe Val Gly Arg Leu Ile Gly Lys Glu Gly Arg			
	290	295	300
Asn Leu Lys Lys Ile Glu Gln Asp Thr Asp Thr Lys Ile Thr Ile Ser			
305	310	315	320
Pro Leu Gln Glu Leu Thr Leu Tyr Asn Pro Glu Arg Thr Ile Thr Val			
	325	330	335
Lys Gly Asn Val Glu Thr Cys Ala Lys Ala Glu Glu Glu Ile Met Lys			
	340	345	350
Lys Ile Arg Glu Ser Tyr Glu Asn Asp Ile Ala Ser Met Asn Leu Gln			
	355	360	365
Ala His Leu Ile Pro Gly Leu Asn Leu Asn Ala Leu Gly Leu Phe Pro			
	370	375	380
Pro Thr Ser Gly Met Pro Pro Pro Thr Ser Gly Pro Pro Ser Ala Met			
385	390	395	400
Thr Pro Pro Tyr Pro Gln Phe Glu Gln Ser Glu Thr Glu Thr Val His			
	405	410	415
Leu Phe Ile Pro Ala Leu Ser Val Gly Ala Ile Ile Gly Lys Gln Gly			
	420	425	430
Gln His Ile Lys Gln Leu Ser Arg Phe Ala Gly Ala Ser Ile Lys Ile			
	435	440	445
Ala Pro Ala Glu Ala Pro Asp Ala Lys Val Arg Met Val Ile Ile Thr			
	450	455	460
Gly Pro Pro Glu Ala Gln Phe Lys Ala Gln Gly Arg Ile Tyr Gly Lys			
465	470	475	480
Ile Lys Glu Glu Asn Phe Val Ser Pro Lys Glu Glu Val Lys Leu Glu			
	485	490	495
Ala His Ile Arg Val Pro Ser Phe Ala Ala Gly Arg Val Ile Gly Lys			
	500	505	510
Gly Gly Lys Thr Val Asn Glu Leu Gln Asn Leu Ser Ser Ala Glu Val			
	515	520	525
Val Val Pro Arg Asp Gln Thr Pro Asp Glu Asn Asp Gln Val Val Val			
	530	535	540
Lys Ile Thr Gly His Phe Tyr Ala Cys Gln Val Ala Gln Arg Lys Ile			
545	550	555	560
Gln Glu Ile Leu Thr Gln Val Lys Gln His Gln Gln Gln Lys Ala Leu			
	565	570	575
Gln Ser Gly Pro Gln Ser Arg Arg Lys			
	580	585	

<210> 428
 <211> 1764
 <212> DNA
 <213> Homo sapiens

<400> 428
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 ctggtgaaga ctggctacgc gttcgtggac tgcccggacg agagctgggc cctcaaggcc 180
 atcgaggcgc tttcaggtaa aatagaactg caccggaaaac ccatagaagt tgagcactcg 240
 gtcccaaaaa ggcaaggat tcggaaactt cagatacgaa atatcccgcc tcatttacag 300
 tgggaggtgc tggatagttt actagtccag tatggagtgg tggagagctg tgagcaagtg 360
 aacactgact cggaaactgc agttgtaaat gtaacctatt ccagtaagga ccaagctaga 420
 caagcactag acaaaactgaa tggatttcag ttagagaatt tcaccttgaa agtagcctat 480
 atocctgatg aaacggccgc ccagcaaaac cccttgacg agccccgagg tcgccggggg 540
 cttgggcaga ggggctcctc aaggcagggg tctccaggat ccgtatccaa gcagaaacca 600
 tgtgatttgc ctctgcgcct gctggttccc acccaatttg ttggagccat cataggaaaa 660
 gaaggtgcca ccattcggaa catcacaaa cagaccagct ctaaaatcga tgtccaccgt 720
 aaagaaaaatg cgggggctgc tgagaagtcg attactatcc tctctactcc tgaaggcacc 780
 tctgcggtt gtaagtctat tctggagatt atgcataagg aagctcaaga tataaaattc 840
 acagaagaga tccccttgaa gatttttagct cataataact ttgttgacg tcttatttgt 900
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 gatattgctt ctatgaatct tcaagcacat ttaattcctg gattaaatct gaacgccttg 1140
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 gtgccatcct ttgtgctgg cagagttatt ggaaaaggag gcaaaacggt gaatgaactt 1560
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 caagtgttg tcaaaataac tggctacttc tatgcttgcc aggttgccca gagaaaaatt 1680
 caggaaattc tgactcaggt aaagcagcac caacaacaga aggtcttgca aagtggacca 1740
 cctcagtcga gacggaagta atga 1764

<210> 429
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 429
 ccatggaatt cattatttca atataagata atctc

35

<210> 430
 <211> 881
 <212> PRT
 <213> Homo sapiens

<400> 430
 Met Gln His His His His His Gly Val Gln Leu Gln Asp Asn Gly
 1 5 10 15
 Tyr Asn Gly Leu Leu Ile Ala Ile Asn Pro Gln Val Pro Glu Asn Gln

[illegible]

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<210> 431
<211> 2646
<212> DNA
<213> Homo sapiens
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<400> 431

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atgataactg aagcttcatt ttacctatct aatgctacca agagaagagt atttttcaga 180
aatataaaga ttttaatacc tgccacatgg aaagctaata ataacagcaa aataaaacaa 240
gaatcatatg aaaaggcaaa tgtcatagtg actgactggg atggggcaca tggagatgat 300
ccatacacc tacaatacag aggggtgtgga aaagaggaa aatacattca tttcacacct 360
aatttcctac tgaatgataa cttaacagct ggctacggat cacgaggccg agtgtttgtc 420
catgaatggg cccacctocg ttgggggtgtg ttcgatgagt ataacaatga caaacctttc 480
tacataaatg ggcaaaatca aattaaagtg acaagggtgt catctgacat cacaggcatt 540
tttgtgtgtg aaaaagggtcc ttgcccccaa gaaaactgta ttattagtaa gctttttaaa 600
gaaggatgca cctttatcta caatagcacc caaaatgcaa ctgcatcaat aatgttcatt 660
caaagtttat cttctgtgtg tgaattttgt aatgcaagta cccacaacca agaagcacca 720
aacctacaga accagatgtg cagcctcaga agtgcattgg atgtaatcac agactctgct 780
gactttcacc acagctttcc catgaacggg actgagcttc cacctcctcc cacattctcg 840
ctgtgtaggg ctggtgacaa agtgggtctg ttagtgtcgg atgtgtccag caagatggca 900
gaggctgaca gactccttca actacaacaa gccgcagaat tttatttgat gcagattgtt 960
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gttgcaatac gagcaatgga taggaactcc ttacagtctg ctgtatctaa cattgcccag 2580
gcgcctctgt ttattccccc caattctgat cctgtacctg ccagagatta tcttatattg 2640
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<210> 432

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 432

gcgcctctcg agtcattaat attcatcaga aaatgg

36

<210> 433
 <211> 371
 <212> PRT
 <213> Homo sapiens

<400> 433

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 20          25          30
Thr Gln Pro Glu Asp Asp Ile Asn Thr Gln Arg Lys Lys Ser Gln Glu
 35          40          45
Lys Met Arg Glu Val Thr Asp Ser Pro Gly Arg Pro Arg Glu Leu Thr
 50          55          60
Ile Pro Gln Thr Ser Ser His Gly Ala Asn Arg Phe Val Pro Lys Ser
 65          70          75          80
Lys Ala Leu Glu Ala Val Lys Leu Ala Ile Glu Ala Gly Phe His His
 85          90          95
Ile Asp Ser Ala His Val Tyr Asn Asn Glu Glu Gln Val Gly Leu Ala
 100         105         110
Ile Arg Ser Lys Ile Ala Asp Gly Ser Val Lys Arg Glu Asp Ile Phe
 115         120         125
Tyr Thr Ser Lys Leu Trp Ser Asn Ser His Arg Pro Glu Leu Val Arg
 130         135         140
Pro Ala Leu Glu Arg Ser Leu Lys Asn Leu Gln Leu Asp Tyr Val Asp
 145         150         155         160
Leu Tyr Leu Ile His Phe Pro Val Ser Val Lys Pro Gly Glu Glu Val
 165         170         175
Ile Pro Lys Asp Glu Asn Gly Lys Ile Leu Phe Asp Thr Val Asp Leu
 180         185         190
Cys Ala Thr Trp Glu Ala Met Glu Lys Cys Lys Asp Ala Gly Leu Ala
 195         200         205
Lys Ser Ile Gly Val Ser Asn Phe Asn His Arg Leu Leu Glu Met Ile
 210         215         220
Leu Asn Lys Pro Gly Leu Lys Tyr Lys Pro Val Cys Asn Gln Val Glu
 225         230         235         240
Cys His Pro Tyr Phe Asn Gln Arg Lys Leu Leu Asp Phe Cys Lys Ser
 245         250         255
Lys Asp Ile Val Leu Val Ala Tyr Ser Ala Leu Gly Ser His Arg Glu
 260         265         270
Glu Pro Trp Val Asp Pro Asn Ser Pro Val Leu Leu Glu Asp Pro Val
 275         280         285
Leu Cys Ala Leu Ala Lys Lys His Lys Arg Thr Pro Ala Leu Ile Ala
 290         295         300
Leu Arg Tyr Gln Leu Gln Arg Gly Val Val Val Leu Ala Lys Ser Tyr
 305         310         315         320
Asn Glu Gln Arg Ile Arg Gln Asn Val Gln Val Phe Glu Phe Gln Leu
 325         330         335
Thr Ser Glu Glu Met Lys Ala Ile Asp Gly Leu Asn Arg Asn Val Arg
 340         345         350
Tyr Leu Thr Leu Asp Ile Phe Ala Gly Pro Pro Asn Tyr Pro Phe Ser
 355         360         365
Asp Glu Tyr
 370

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<210> 434
 <211> 1119

<212> DNA

<213> Homo sapiens

<400> 434

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acacagagga	agaagagtca	ggaaaagatg	agagaagtta	cagactctcc	tgggcgaccc	180
cgagagctta	ccattcctca	gacttcttca	catggtgcta	acagatttgt	tcctaaaagt	240
aaagctctag	aggccgtcaa	attggcaata	gaagccgggt	tccaccatat	tgattctgca	300
catgtttaca	ataatgagga	gcaggttgga	ctggccatcc	gaagcaagat	tgagatggc	360
agtgtgaaga	gagaagacat	attctacact	tcaaagcttt	ggagcaattc	ccatcgacca	420
gagttgggtcc	gaccagcctt	ggaaagggtca	ctgaaaaatc	ttcaattgga	ctatgttgac	480
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aatgagcagc	gcacagaca	gaacgtgcag	gtgtttgaat	tccagttgac	ttcagaggag	1020
atgaaagcca	tagatggcct	aaacagaaat	gtgcgatatt	tgacccttga	tatttttgct	1080
ggcccccta	attatccatt	ttctgatgaa	tattaatga			1119

<210> 435

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 435

ggatccgccg	ccaccatgac	atccattcga	gctgta	36
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<210> 436

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 436

gtcgactcag	ctggaccaca	gccgcag	27
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<210> 437

<211> 37

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 437

ggatccgccg	ccaccatgga	ctcctggacc	ttctgct	37
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<210> 438

<211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Primer

<400> 438
 gtcgactcag aaatcctttc tcttgac

27

<210> 439
 <211> 933
 <212> DNA
 <213> Homo sapiens

<400> 439
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 agatgtaaac caatttcagg acacgactac cttttctggt acagacagac catgatgcgg 180
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<210> 440
 <211> 822
 <212> DNA
 <213> Homo sapiens

<400> 440
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 aagtgtactt attcagacag tgcctcaaac tacttccctt ggtataagca agaacttga 180
 aaaagacctc agcttattat agacattcgt tcaaatgtgg gcgaaaagaa agaccaacga 240
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 cctgaagact cggctgtcta cttctgtgca gcaagtatac tgaacaccgg taaccagttc 360
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 gtgtaccagc tgagagactc taaatccagt gacaagtctg tctgcctatt caccgatttt 480
 gattctcaaa caaatgtgtc acaaagtaag gattctgatg tgtatatcac agacaaaact 540
 gtgctagaca tgaggtctat ggacttcaag agcaacagtg ctgtggcctg gagcaacaaa 600
 tctgactttg catgtgcaaa cgccttcaac aacagcatta ttccagaaga caccttcttc 660
 cccagcccag aaagtctctg tgatgtcaag ctggtcgaga aaagctttga aacagatacg 720
 aacctaaact ttcaaaacct gtcagtattt gggttccgaa tctctctcct gaaagtggcc 780
 gggtttaatc tgctcatgac gctgcggctg tgggtccagct ga 822

<210> 441
 <211> 2311
 <212> DNA

<213> Homo sapiens

<400> 441

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aagagttggg gtttgctcag gaagagattt aagcatgctt gcttaaccag actcagagaa 120
gtctccctgt tctgtcctag ctatgttcct gtgttgtgtg cattcgtctt ttccagagca 180
aaccgcccag agtagaagat ggattggggc acgctgcaga cgatcctggg ggggtgtgaa 240
aaacactcca ccagcattgg aaagatctgg ctacccgtcc tcttcatttt tcgcattatg 300
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tttaaggaca tcgaggagat caaaaccag aaggtccgca tcgaaggctc cctgtgtggg 600
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atttaaaaca ttaaaatata atctctataa t 2311

```

<210> 442

<211> 226

<212> PRT

<213> Homo sapiens

<400> 442

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Met Asp Trp Gly Thr Leu Gln Thr Ile Leu Gly Gly Val Asn Lys His
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Ser Thr Ser Ile Gly Lys Ile Trp Leu Thr Val Leu Phe Ile Phe Arg
      20              25              30

Ile Met Ile Leu Val Val Ala Ala Lys Glu Val Trp Gly Asp Glu Gln
      35              40              45

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[illegible]

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<210> 443
<211> 23
<212> PRT
<213> Homo sapiens
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<400> 443
Val Lys Leu Cys Gly Ile Asp Pro Cys Pro Asn Leu Val Asp Cys Phe
 5 10 15

Ile Ser Arg Pro Gly Cys Gly
20

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<210> 444
<211> 36
<212> DNA
<213> Artificial Sequence
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<220>
<223> PCR primer

<400> 444

caatcaggca tgcacaacaa actgtatatc ggaaac

36

<210> 445

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 445

cgtcaagatc ttcattactt ccgtcttgac

30

<210> 446

<211> 579

<212> PRT

<213> Homo sapiens

<400> 446

Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
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20 25 30Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser
35 40 45Trp Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His
50 55 60Gly Lys Pro Ile Glu Val Glu His Ser Val Pro Lys Arg Gln Arg Ile
65 70 75 80Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu Val
85 90 95Leu Asp Ser Leu Leu Val Gln Tyr Gly Val Val Glu Ser Cys Glu Gln
100 105 110Val Asn Thr Asp Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Ser
115 120 125Lys Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu
130 135 140Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro Asp Glu Thr Ala Ala
145 150 155 160Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly Gln
165 170 175Arg Gly Ser Ser Arg Gln Gly Ser Pro Gly Ser Val Ser Lys Gln Lys
180 185 190

Pro Cys Asp Leu Pro Leu Arg Leu Leu Val Pro Thr Gln Phe Val Gly
 195 200 205
 Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
 210 215 220
 Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
 225 230 235 240
 Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala Ala
 245 250 255
 Cys Lys Ser Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys
 260 265 270
 Phe Thr Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
 275 280 285
 Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu Gln
 290 295 300
 Asp Thr Asp Thr Lys Ile Thr Ile Ser Pro Leu Gln Glu Leu Thr Leu
 305 310 315 320
 Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Asn Val Glu Thr Cys
 325 330 335
 Ala Lys Ala Glu Glu Glu Ile Met Lys Lys Ile Arg Glu Ser Tyr Glu
 340 345 350
 Asn Asp Ile Ala Ser Met Asn Leu Gln Ala His Leu Ile Pro Gly Leu
 355 360 365
 Asn Leu Asn Ala Leu Gly Leu Phe Pro Pro Thr Ser Gly Met Pro Pro
 370 375 380
 Pro Thr Ser Gly Pro Pro Ser Ala Met Thr Pro Pro Tyr Pro Gln Phe
 385 390 395 400
 Glu Gln Ser Glu Thr Glu Thr Val His Leu Phe Ile Pro Ala Leu Ser
 405 410 415
 Val Gly Ala Ile Ile Gly Lys Gln Gly Gln His Ile Lys Gln Leu Ser
 420 425 430
 Arg Phe Ala Gly Ala Ser Ile Lys Ile Ala Pro Ala Glu Ala Pro Asp
 435 440 445
 Ala Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe
 450 455 460
 Lys Ala Gln Gly Arg Ile Tyr Gly Lys Ile Lys Glu Glu Asn Phe Val
 465 470 475 480
 Ser Pro Lys Glu Glu Val Lys Leu Glu Ala His Ile Arg Val Pro Ser
 485 490 495
 Phe Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu
 500 505 510

Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr
515 520 525

Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr
530 535 540

Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val
545 550 555 560

Lys Gln His Gln Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser
565 570 575

Arg Arg Lys

<210> 447

<211> 1743

<212> DNA

<213> Homo sapiens

<400> 447

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ttcgtggact gcccgacga gagctgggccc ctcaaggcca tcgaggcgct ttcaggtaaa 180
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gttgtaaatg taacctattc cagtaaggac caagctagac aagcactaga caaactgaat 420
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<210> 448

<211> 35

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 448

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35

<210> 449

<211> 579

<212> PRT

<213> Homo sapiens

<400> 449

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Met Asn Lys Leu Tyr Ile Gly Asn Leu Ser Glu Asn Ala Ala Pro Ser
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Asp Leu Glu Ser Ile Phe Lys Asp Ala Lys Ile Pro Val Ser Gly Pro
      20                      25                      30

Phe Leu Val Lys Thr Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu Ser
      35                      40                      45

Trp Ala Leu Lys Ala Ile Glu Ala Leu Ser Gly Lys Ile Glu Leu His
      50                      55                      60

Gly Lys Pro Ile Glu Val Glu His Ser Val Pro Lys Arg Gln Arg Ile
      65                      70                      75                      80

Arg Lys Leu Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu Val
      85                      90                      95

Leu Asp Ser Leu Leu Val Gln Tyr Gly Val Val Glu Ser Cys Glu Gln
      100                     105                     110

Val Asn Thr Asp Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Ser
      115                     120                     125

Lys Asp Gln Ala Arg Gln Ala Leu Asp Lys Leu Asn Gly Phe Gln Leu
      130                     135                     140

Glu Asn Phe Thr Leu Lys Val Ala Tyr Ile Pro Asp Glu Thr Ala Ala
      145                     150                     155                     160

Gln Gln Asn Pro Leu Gln Gln Pro Arg Gly Arg Arg Gly Leu Gly Gln
      165                     170                     175

Arg Gly Ser Ser Arg Gln Gly Ser Pro Gly Ser Val Ser Lys Gln Lys
      180                     185                     190

Pro Cys Asp Leu Pro Leu Arg Leu Leu Val Pro Thr Gln Phe Val Gly
      195                     200                     205

Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
      210                     215                     220

Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
      225                     230                     235                     240

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Glu Lys Ser Ile Thr Ile Leu Ser Thr Pro Glu Gly Thr Ser Ala Ala
 245 250 255
 Cys Lys Ser Ile Leu Glu Ile Met His Lys Glu Ala Gln Asp Ile Lys
 260 265 270
 Phe Thr Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
 275 280 285
 Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu Gln
 290 295 300
 Asp Thr Asp Thr Lys Ile Thr Ile Ser Pro Leu Gln Glu Leu Thr Leu
 305 310 315 320
 Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Asn Val Glu Thr Cys
 325 330 335
 Ala Lys Ala Glu Glu Glu Ile Met Lys Lys Ile Arg Glu Ser Tyr Glu
 340 345 350
 Asn Asp Ile Ala Ser Met Asn Leu Gln Ala His Leu Ile Pro Gly Leu
 355 360 365
 Asn Leu Asn Ala Leu Gly Leu Phe Pro Pro Thr Ser Gly Met Pro Pro
 370 375 380
 Pro Thr Ser Gly Pro Pro Ser Ala Met Thr Pro Pro Tyr Pro Gln Phe
 385 390 395 400
 Glu Gln Ser Glu Thr Glu Thr Val His Leu Phe Ile Pro Ala Leu Ser
 405 410 415
 Val Gly Ala Ile Ile Gly Lys Gln Gly Gln His Ile Lys Gln Leu Ser
 420 425 430
 Arg Phe Ala Gly Ala Ser Ile Lys Ile Ala Pro Ala Glu Ala Pro Asp
 435 440 445
 Ala Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe
 450 455 460
 Lys Ala Gln Gly Arg Ile Tyr Gly Lys Ile Lys Glu Glu Asn Phe Val
 465 470 475 480
 Ser Pro Lys Glu Glu Val Lys Leu Glu Ala His Ile Arg Val Pro Ser
 485 490 495
 Phe Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu
 500 505 510
 Leu Gln Asn Leu Ser Ser Ala Glu Val Val Val Pro Arg Asp Gln Thr
 515 520 525
 Pro Asp Glu Asn Asp Gln Val Val Val Lys Ile Thr Gly His Phe Tyr
 530 535 540
 Ala Cys Gln Val Ala Gln Arg Lys Ile Gln Glu Ile Leu Thr Gln Val

Lys Gln His Gln Gln Gln Lys Ala Leu Gln Ser Gly Pro Pro Gln Ser

565 570 575

Arg Arg Lys

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<210> 450
<211> 1743
<212> DNA
<213> Homo sapiens
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